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THE MAGAZINE OF UT SOUTHWESTERN MEDICAL CENTER

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After undergoing a routine hernia operation, Anita Vasquez returned to her Fort Worth home only to come down with a fever and cough. A simple chest X-ray revealed a nightmarish scenario: Mrs. Vasquez learned she was facing a tumor that threatened to burst out of her lung and invade other organs. Never having touched a cigarette, she and her husband were shocked. "The doctor offered to show me a picture of my left lung on the computer," the 68-year-old former unit secretary at Harris Methodist Hospital recalled recently. "And there it was: a round shadow." The couple immediately started polling friends and family about where to go for treatment. A dietitian at work quietly said she should go to Dallas, specifically to UT Southwestern Medical Center's Harold C. Simmons Cancer Center, which has an excellent lung cancer program. She prayed. But it wasn't until standing in a checkout line the next day that she heard another customer speaking highly of the Simmons Cancer Center.

"It was more than a coincidence that I was in line with this man," Mrs. Vasquez said one recent afternoon. "That's when God intervened and made my decision for me."

She would go to Dallas.

Patients are bringing their cancer fight to the Simmons Cancer Center daily. For some who are emotionally prepared and intellectually curious enough to see cancer up close, the center allows patients to get smart about the disease, in ways that other cancer centers without equally strong research underpinnings cannot. In order to effectively fight an enemy, one must see it to treat it. This is where doctors and scientists at UT Southwestern are making headway every day.

Seeing the enemy

Dr. Adi Gazdar and other Simmons Cancer Center specialists believe that seeing the cancer on a molecular level is important, and not just for the diagnostician. Dr. Gazdar, professor of pathology, holds the W. Ray Wallace Distinguished Chair in Molecular Oncology Research at UT Southwestern.

To most patients, the cancers growing in the flasks and petri dishes that fill Dr. Gazdar's laboratory will remain an invisible enemy. Yet the clumps of non-small cell lung cancers, giant-cell carcinomas and tumors are visible to the naked eye. Hold the flask up to any fluorescent light and they make cancer very real and very alive.

Cynthia Gonzalez was in her early 50s when diagnosed with advanced lung cancer, only after developing a persistent cough that was first thought by doctors to be bronchitis or pneumonia. After multiple visits at another facility and an ineffective course of antibiotics, doctors discovered the truth. A biopsy done at UT MD Anderson Cancer Center in Houston revealed Stage 4 lung cancer.

"By this time I had zero trust in doctors," Mrs. Gonzalez said. "They did give me a video and a brochure and that told me what to expect, but I didn't feel like I was getting the personal attention that I needed."

After asking some friends in the medical community where she could go for the trust and individualized treatment she was seeking, she contacted Dr. Joan Schiller, chief of the Hematology/Oncology Division at UT Southwestern and holder of the Andrea L. Simmons Distinguished Chair in Cancer Research

Mrs. Gonzalez remembers the day vividly. It was Dec. 27, 2010.

"Dr. Schiller called me back that day from her family vacation in Colorado," Mrs. Gonzalez said. "My experience is that most doctors care about their own time, so I was so surprised and encouraged that she would be so selfless."

Mrs. Gonzalez's experience at the Simmons Cancer Center is typical of many patients. The process usually starts with lab tests. Tumor tissue is analyzed every way possible under the microscope and through a series of highly sophisticated molecular assays. Then, using the state-of-the-art information collected at a cellular level, cancer specialists select the best therapy for that patient – what types of chemotherapy drugs and, if indicated, the most effective uses of radiation, what doctors call a "combined modality" treatment.

Understanding the enemy

In scientific terms, cancer is a disease of pathological hyperplasia – uncontrolled growth of the body's own cells. And some patients' interest in the disease – ultimately a fight against their own body – can be comprehensive in itself: Doctors say the informed patient tries to absorb as much information as possible about the latest clinical advances and the most cutting-edge research in cancer biology, applying what they learn to fight their cancer in ways that make sense for them.

At the Simmons Cancer Center, cancer patients can visit the labs to understand more about the enemy, said Dr. John Minna, director of the Nancy B. and Jake L. Hamon Center for Therapeutic Oncology Research and the W.A. "Tex" and Deborah Moncrief Jr. Center for Cancer Genetics. A cancer patient being treated can not only see cancer cells, but has the chance to watch them swarm and multiply in Dr. Gazdar's lab.

"We do have patients who want to consider the totality of their disease and attack it from all angles," said Dr. Minna, a professor of internal medicine, who holds the Sarah M. and Charles E. Seay Distinguished Chair in Cancer Research and the Max L. Thomas Distinguished Chair in Molecular Pulmonary Oncology. "To these patients, visualizing the 'enemy' and understanding it on a fundamental level can increase their interest in shaping a treatment that ultimately improves the outcome."

Call it a personalized, team-based approach that puts the patient on par with the oncologists, researchers, nurses and supportive care personnel who are all dedicated to the fight.



An Invisible enemy

The Simmons Cancer Center is the only cancer center in North Texas to have received a designation from the National Cancer Institute (NCI). While the center is on the cutting edge of detecting and imaging cancer, the problem of adequately seeing cancer on a cellular level dates to when leukemia was known simply as "white blood."

Until the middle of the last century, observing the behavior of cancer cells did not significantly advance until the renowned pediatric pathologist Dr. Sidney Farber first trained his microscope in Boston on the blood of very sick children suffering from an explosion in their white blood cell counts. The blood looked milky under the microscope; he was seeing leukemia. It was 1947, around the time when UT Southwestern as it is known now was just getting off the ground, thanks to the inimitable leadership of Drs. Edward Cary, Donald Seldin and others.

Fast-forward to 2012.

The landscape for detecting, studying and treating cancer has changed radically. Many of the advances are on full display at the Simmons Cancer Center, particularly in the fight against lung cancer, the nation's top cancer killer. More than 173,000 new cases of lung cancer are

Dr. Gazdar is among a select group of cancer scientists searching for lung cancer biomarkers in people who have never smoked. In 2009, the National Cancer Institute's Early Detection Research Network and the Canary Foundation, a nonprofit organization that funds research in early cancer detection, provided initial funding of \$1 million to UT Southwestern for the first year of a biomarker project that is being conducted at five sites across the country. The clinical problem is that lung cancer often cannot be detected until its advanced stages, and the average life expectancy of

Dr. Adi Gazdar scrutinizes a flask for clumps of cancer cells visible with the naked eye. Dr. Gazdar's laboratory has cataloged and analyzed over 2,200 human cancer specimens, with an emphasis on lung cancer and lymphomas.

diagnosed each year in the U.S., accounting for 13 percent of new cancer cases, according to the American Cancer Society. That is equal to the entire city of Dayton, Ohio, getting a diagnosis - when 88 percent of the people living there do not even smoke.

Peter Jennings, the late and pioneering ABC News anchor, smoked. While he passed away quietly in the palliative care unit of Memorial Sloan-Kettering Cancer Center in 2005, no amount of money or expert care could save him. A number of other celebrities and notable personalities have succumbed to lung cancer, smokers and non-smokers alike: Dana Reeve, the wife of actor Christopher Reeve; actors Steve McQueen and Vincent Price; and singer Lou Rawls.

someone receiving a lung cancer diagnosis is less than five years. It is a swift and stealthy killer, often with no early symptoms. And unlike mammography for breast cancer, colonoscopy for colon cancer or PSA tests for prostate cancer, there is no routine screening test for early lung cancer.

Mrs. Vasquez's physician, Dr. Schiller, is trying to fix that.

"The need for a comprehensive and prescribed way of detecting lung cancer early is crucial," Dr. Schiller, professor of internal medicine said. "Older ways of screening just aren't effective at catching lung cancer before it's too late."

A study published Oct. 26, 2011, in the Journal of the American Medical Association found that routine chest X-rays do not reduce the risk of death from lung cancer in smokers or former smokers. The NCI study involved more than 150,000 older Americans. The finding was startling: Those who had annual chest X-ray screenings over four years were just as likely to die of lung cancer as study volunteers who did not get screened. In other words, chest X-rays are not useful in preventing lung cancer or seeing it early enough.



Dr. Joan Schiller and her colleagues have established a chest CT scanning program at UT Southwestern aimed at current and prior smokers ages 55 years and older. The screening helps identify cancers before they become a serious problem.

The findings suggest the best strategy for discovering lung tumors in an early, more treatable stage is screening with computed tomography (CT) scans, which were shown in a separate recent study to lower the death rate by 20 percent.

To detect lung cancer earlier, the team led by Dr. Schiller, Dr. Kemp Kernstine, Chair of the Division of Thoracic Surgery and holder of Robert Tucker Hayes Foundation Distinguished Chair in Cardiothoracic Surgery, and Dr. Hak Choy, chair of the Department of Radiation Oncology and holder of the Nancy B. and Jake L. Hamon Distinguished Chair in Therapeutic Oncology Research, have started a chest CT screening program that allows qualified people who are at risk to elect to have a spiral CT scan done. Team members Dr. Muhanned Abu-Hijleh, associate professor of internal medicine, and Dr. Cecelia Brewington, professor of radiology, designed the program, which also has a research component to identify other means for detecting cancer earlier, in the breath, saliva, mouth cells and blood.

While preventative CT scans are not yet covered by insurance, they are recommended for current and prior smokers ages 55 and older. The test consists of one low-dose CT scan per year for three years. Lung cancer is not the only potentially life-threatening disease the scan is able to detect. While scanning for lung cancer, CT scans also can reveal the presence of other diseases, such as heart disease, emphysema and other cancers that may originate in or have spread to the chest.

"There are some caveats, but this represents an opportunity to catch lung cancer and other diseases very early, well before they become a serious problem," Dr. Schiller said.

Nearly a quarter of the patients will be found to have suspicious findings, most of them not cancer. While patients are exposed to low doses of radiation, each scan's radiation dose is less than a fifth of the dose of regular CT scans.

The key is to see the cancer while there is still time to do something about it, Dr. Schiller said. In Mrs. Vasquez's case, there was still time but the window was rapidly closing.

Attacking the enemy

UT Southwestern leads a SPORE (Specialized Programs of Research Excellence) grant that is shared with MD Anderson. Such grants are the cornerstone of the NCI's effort to promote collaborative, interdisciplinary cancer research and treatment. These grants involve both basic scientists and clinicians working on new ways

Lung cancer biology: getting down to the DNA

Radiation therapy is a powerful tool in treating cancer, but as many patients can attest, being treated with radiation is not without side effects.

"Radiation is a double-edged sword that affects both tumors and healthy tissues," says Dr. Hak Choy, chairman of radiation oncology and holder of the Nancy B. and Jake L. Hamon Distinguished Chair in Therapeutic Oncology Research. "Therefore, it is imperative that we administer radiation as carefully and as precisely as possible. If we didn't have to worry about the side effects of radiation, we could cure almost any cancer."

In order to deliver the most precise and least harmful doses of radiation, the university's Department of Radiation Oncology has invested in leading-edge devices capable of treating cancers anywhere in the body (see "Brave New World: High Tech Medicine" on p. 18), while ensuring minimal damage to surrounding healthy tissue. The result is fewer side effects for treatments that 10 years ago would have been associated with extreme fatigue, skin changes, hair loss, mouth problems and more.

But these are only the visible effects of radiation. Radiation therapy works by deliberately damaging the cellular DNA, which ultimately induces tumor cell death. While



studying how DNA is repaired by the body, with an eye toward mitigating the side effects of radiation and more effectively targeting tumors.

DNA damage to the tumor is desirable, healthy tissue may also be subjected to DNA damage, which may result in side effects ranging from temporary irritation, to scarring, necrosis and even (in the long term) giving rise to new cancers.

Understanding how tumor and healthy tissue repair DNA damage is an area that may significantly impact the future ability of physicians to mitigate such side effects while more effectively targeting tumors.

In March, the Cancer Prevention and Research Institute of Texas (CPRIT) awarded \$6.4 million to a multi-institutional group led by a UT Southwestern researcher who has made historic contributions to the field of DNA repair. Dr. David Chen, chief of

the division of molecular radiation biology and holder of the David A. Pistenmaa, M.D., Ph.D., Distinguished Professorship in Radiation Oncology, leads the five-year project to identify the molecular events that underlie the choice between pathways for repairing DNA double-strand breaks (DSBs).

Although normal human cells are exposed to multiple DNA lesions every day, the type of damage inflicted by radiation double-strand breaks - is the most harmful. In this instance, both pairs of genes are broken, increasing the likelihood

that the cell will either be unable to repair itself or that the genetic code will pass on damaged information during cell replication.

Human cells have two distinct methods to repair DSBs, and one of the major unresolved questions in the field of DNA research is what mechanism determines the choice between the two. The importance of these repair pathways is supported by the observation that an increase in cancer incidence is associated with impaired DSB repair.

"The increased level of DNA damage in cancer cells and the use of DNA-damaging agents in cancer treatment underlie the importance of DSB repair in cancer biology," Dr. Chen says. "Basic mechanistic insights into DSB repair mechanisms and

the regulation of pathway choice for the repair of DSBs are likely to translate into new opportunities for cancer treatment."

With the CPRIT money awarded to UT Southwestern, Dr. Benjamin Chen, assistant professor of radiation oncology together with Dr. David Chen, will investigate whether activity at a specific amino acid cluster (the T2609 cluster) plays a role in determining pathway choice. Another university researcher, Dr. Hongtao Yu, professor of pharmacology, a Howard Hughes Medical Institute investigator and a Michael L. Rosenberg Scholar in Medical Research, will study regulation of the DNA repair pathway choice by two other protein complexes that are involved in cell replication. Their individual projects are funded at \$1.3 million each.

Dr. John Minna believes that UT Southwestern's edge in personalized care comes from tailoring treatment options to a molecular analysis of each patient's tumor.



to prevent, detect and diagnose cancers, as well as to treat them. The Simmons Cancer Center is now headlong into an effort to identify the molecular hallmarks of lung cancer, with an eye toward developing better drugs.

The goal is to further personalize the therapeutic options available to individual cancer patients who may be facing common cancers with a unique set of characteristics. When combined with state-of-the-art methods to test compounds against hundreds of different combinations of genetic mutations, a cure for certain cancers, such as lung, may be within reach.

Dr. Michael White, professor of cell biology, who is focused on uncovering the mechanisms by which cells can adversely react to their own environment, said this represents a departure from the "guess-and-test" approach that has characterized a lot of the cancer biology that eventually moved into the clinical realm.

Rather than "throwing spaghetti at the walls to see what sticks," Dr. White, who holds the Sherry Wigley Crow Cancer Research Endowed Chair, in Honor of Robert Lewis Kirby, M.D. and the Grant A. Dove Chair for Research in Oncology, said UT Southwestern researchers as well as colleagues elsewhere are tapping into an array of genetics assays, cell lines and tumor models that have exclusively been built at UT Southwestern over the years.

Collaborating with leaders in biochemistry and pharmacology, Dr. White and his colleagues, Dr. Michael Roth, the interim dean of UT Southwestern Graduate School of Biomedical Sciences and vice chairman of biochemistry who holds the Diane and Hal Brierley Distinguished Chair in Biomedical

Research; Dr. Bruce Posner, associate professor of biochemistry; and Dr. Minna are supported by large grants from the National Cancer Institute and the Cancer Prevention and Research Institute of Texas (CPRIT).

CPRIT has allowed these researchers to cross-test thousands of different compounds and biological agents against different cancers ranging from the ordinary to the exotic.

As Dr. White points out, "combining our high-throughput screening results with all of the molecular information we have assembled on lung cancers allows us to determine many new therapeutic targets, which will change how we approach lung cancer. This will also allow us to 'personalize' the use of these new therapies by finding the right molecular match for each patient's tumor – something we refer to as 'enrollment biomarkers.'"

Researchers here and elsewhere believe that this is the most promising way in which socalled "translational" research is poised to crack the cancer code and "catch up" with biology.

"The doctors at UT Southwestern used a combination of drugs that was specifically tailored for my particular cancer," Mrs. Gonzalez said. "I think the drugs that my other doctors would have put me on would not have been as effective."

Outwitting the enemy

Since feelings can be hard to see, the emotional component of a positive diagnosis is often the most difficult aspect of cancer to fully appreciate. The marshaling of spiritual resources needed to take on a war against

cancer is a battle with which Mrs. Vasquez and Mrs. Gonzalez are intimately familiar.

"Patients often are looking for things that give them hope and a sense of control," said Dr. Simon Craddock Lee, a medical anthropologist who focuses on cancer disparities and patient decision-making, and a member of the Population Sciences and Cancer Control Program within the Simmons Cancer Center. "Oncologists do their best to communicate the options for patients while supporting them in their right to decide the best course of treatment. In comprehensive cancer care, a cadre of experts works with oncologists to try to address all the different needs of a patient."

To this end, the Simmons Cancer Center has a growing, multifaceted support program designed to work in concert with oncologists and their patients from the very moment of diagnosis.

"This is where our program is distinct from other cancer care support programs," said Dr. Jeff Kendall, associate professor of psychiatry and the clinical leader of the supportive services program at the center. "Rather than being mentioned as an afterthought to treatment, we bring support services to the fore right away, as a seamless complement to treating the whole patient, perhaps before he or she even realizes it is necessary."

The new direction in cancer care today is treating the "whole patient," Dr. Kendall notes. This treatment model means recognizing the importance of the emotional, social and spiritual changes that often accompany a devastating diagnosis of cancer and the effect the illness can have on an entire family.

However, recognition is not enough. It is just as important to intervene once certain needs have been identified, he said.

Efforts by Dr. Kendall and his staff have sought to raise awareness and identify emotional issues in cancer care through "psychosocial distress screening" interviews with patients. In a sense, Dr. Kendall is attempting to see any signs of distress in his patients while there is time to intervene.

The stress associated with a cancer diagnosis has been shown to cause considerable psychological morbidity, with 25 percent to 50 percent of all cancer patients indicating significant levels of distress.

"While our advances in cancer research and treatment continue at a steady pace, patients now face more complex treatment decisions and follow-up options," said Dr. James K.V. Willson, director of the Simmons Cancer Center and holder of the Lisa K. Simmons



The Harold C. Simmons Cancer Center is one of only seven in the nation to obtain a prestigious Specialized Program of Research Excellence (SPORE) grant from the National Cancer Institute.

Distinguished Chair in Comprehensive Oncology. "UT Southwestern has a caring staff of medical professionals who are committed to enhancing patients' quality of life, as well as meeting the needs of patients' families. A key component of our mandate as an NCIdesignated cancer facility is that we meet all aspects of a patient's total care. Support services are a key element in that."

After undergoing a lobectomy to remove the part of her lung that was cancerous, followed by a chemotherapy and radiation regimen at the Simmons Cancer Center, Mrs. Vasquez still sees her doctors regularly.

"When I was diagnosed and decided to start going to UT Southwestern, people said, 'Why do you keep going there? It's too far!'" she recently recounted. "The fact that I bonded so well with Dr. Schiller and that they still check on me is why. Of course, having cancer has made me more religious. I thank God for the care I get there."



BY LAKISHA LADSON

The Nation's No.1 Killer Sends Silent Signals

Despite the notion that heart disease occurs without warning, UT Southwestern Medical Center cardiologists are discovering that the nation's No. 1 killer does indeed send silent signals of impending cardiovascular disease decades before seemingly healthy people realize their lives are under assault.

The murderer's many weapons, which include atherosclerosis, heart attack, stroke and congestive heart failure, may be noted through silent cues from blood-based tests, advanced imaging scans and possibly even a person's capacity to exercise.

"We're discovering risk factors that are clear and completely silent," said Dr. Darren McGuire, associate professor of internal medicine at UT Southwestern. "People feel fine even when the classic risk factors for cardiac disease are diagnosed, such as increased blood pressure, abnormal cholesterol or diabetes. Uncovering these silent signals that become abnormal long before disease is evident gives us opportunities to create therapies to intervene before heart disease disables or ends a person's life."



"Though heart disease tends to cluster at older ages, if you want to prevent it, our data is suggesting that the prescription for prevention needs to occur earlier - in people's 30s and 40s." -Dr. Jarett Berry



ology are numerous – open heart surgery, heart transplants, artificial hearts and battery-powered devices to help the heart beat. Doctors can enliven a dying heart, help a heart recover after

dvances in the field of cardi-

suffering an oxygen-deprived attack and clear arteries clogged with dangerous plaque.

When it comes to prevention, however, doctors still rely on risk factors first categorized at the time heart disease was put on the national radar: increasing age, diabetes, smoking cigarettes and having high blood pressure or high cholesterol.

While these measurements, first noted in the mid-20th century, have stood the test of time for groups of people, the current and future age of personalized medicine calls for improved and new tools to assess, predict and then change long-term risk for individuals.

"We're trying to stop people from becoming patients," said Dr. James de Lemos, professor of internal medicine.

Treatment, prevention

Drs. de Lemos and McGuire are leaders on a UT Southwestern team of nearly a dozen cardiologists who care for patients as well as execute research to prevent and alleviate the problems they treat at affiliated hospitals. In 2010, heart disease care in the U.S. cost \$273 billion, and that number is expected to triple by 2030 due to the aging population. The statistics don't include \$172 billion in lost productivity in 2010 and an estimated \$276 billion in 2030.

"Fear is a great motivator," said Dr. de Lemos, who has seen people change lifestyle habits that contributed to their disease. "There is nothing like a heart attack to get somebody to stop smoking or to start exercising, but unfortunately by the time people have their heart attack their disease is already quite advanced."

For men, the average age of a first heart attack is in the 60s, and for women in the 70s.

"Though heart disease tends to cluster at older ages, if you want to prevent it, our data is suggesting that the prescription for prevention needs to occur earlier – in people's 30s and 40s," said Dr. Jarett Berry, assistant professor of internal medicine at UT Southwestern and member of the research team.

Part of their work on the silent signals of heart disease means assessing and tweaking traditional risk factors. It turns out that some people may not know or grasp their increased risk from these signals.

Diabetes, for example, is a risk factor traditionally associated with disease of the eyes and kidneys, but its primary complication is actually heart disease. Dr. McGuire is a national expert on the relationship between the two diseases and an authority for analyzing complex data sets deriving from international multicenter trials. He works to expand the care for patients with diabetes from solely focusing on glucose – only one of many risk factors of diabetes – to the more broad cardiovascular risks associated with the disease and its treatments.

"If we take a one-size-fits-all approach to heart disease, No. 1 we'll run out of ammunition, and No. 2 we'll apply interventions – some of which are expensive, some of which are toxic, some of which consume extensive personnel resources – to people who really never needed them," he said. "Managing the cardiovascular risk factors associated with diabetes – high blood pressure, high blood cholesterol, obesity and physical inactivity – is one way to most efficiently apply our limited resources to target heart disease."

Dr. McGuire and colleagues at UT Southwestern found in a study of randomly selected adults living in Dallas County that about 11 percent of nearly 3,300 participants had diabetes, but more than one-third of them didn't know it.

"Even though diabetes seems to be everywhere, it is almost always underestimated and very dramatically so," Dr. McGuire said. "Therapies proven to reduce the cardiovascular risk associated with diabetes continue to be under used even among people who know they have the disease, and often not used at all in those who are unaware they have diabetes."

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Diabetes is associated with a two- to four-time greater lifetime risk for cardiovascular disease. "The presence of diabetes should key people to get very aggressive with cholesterol and blood pressure management, and lifestyle interventions targeted at weight control and regular leisure-time physical activity," Dr. McGuire said. "And all adults should 'know their numbers:' blood pressure, cholesterol, and fasting glucose, since so often these abnormalities are not diagnosed in the community." Family history is another known traditional risk factor. If someone's grandfather, uncle, and sister all had heart disease, the chance is very likely that they may suffer a similar fate. But UT Southwestern research discovered that women may not do anything about it.



Women at special risk

Research done on more than 2,400 people found that women with a first-degree relative with a history of premature heart attacks (before the age of 50 in men and 55 in women) had more plaque buildup in their arteries than women without such family histories. Yet they were less likely than men to change habits associated with poor health and cardiovascular disease such as smoking cigarettes and not exercising enough.

"Women are twice as likely as men to have fatal heart attacks, and even when they have genetic reasons to change their behavior they're less likely to," said Dr. Amit Khera, associate professor of internal medicine, epidemiologist and leader of UT Southwestern's preventive cardiology program. "Women may need more targeted messages about the importance of family history in order to make the appropriate lifestyle changes because the earlier they do – the more they can decrease their heart disease risk in the future."

UT Southwestern researchers are also working to understand the traditional risk factor of obesity, which is reaching epidemic proportions in the U.S. and is ignored by many overweight people.

Researchers asked more than 2,000 obese people their thoughts about their weight. Eight percent of respondents said they were at the weight they wanted to be at or that they wanted to get larger. Among African-Americans and Hispanics, that statistic rose to 14 percent and 11 percent, respectively.

"We discovered that taking out a tape measure and determining their waist-to-hip ratio is one accurate way to know who we should focus on."

"It's not a rare phenomenon," said Dr. de Lemos, who holds the Sweetheart Ball – Kern Wildenthal, M.D., Ph.D., Distinguished Chair in Cardiology. "Physicians have a lot to learn if we think we can just put platitudes out there about exercise and diet thinking these will hit home for people when they don't even realize they need to lose weight."

These study participants had similar heart disease risk factors as obese people who recognize their need to lose weight, but believed they were at lower risk for hypertension, diabetes and high cholesterol – all factors in heart disease.

The study also asked how many participants had been told by their doctor they needed to lose weight.

"Not many people had been told," Dr. McGuire said. "Does it matter if the doctor and patient are the same sex or race? There is a lot of cultural learning on all sides of the interaction that needs to be improved so people understand that obesity is not a cosmetic preference, but a medical issue."

Dr. de Lemos said the investigation highlighted the complexity of the problem.

"This epidemic is complicated; there are knowledge and cultural factors that are deeply embedded in the community that we need to understand and target specifically if we are going to make a difference," he said.

Risk indicators challenged

The general public, it turns out, may not be the only group without the most accurate information. Health care professionals often use the body-mass-index – a weight-to-height ratio created based on groups of people to determine what range a person's healthy weight should be according to their height. Higher numbers equate to worse cardiovascular outcomes.

But, Drs. de Lemos, McGuire, Khera and others at UT Southwestern found that the waist-to-hip ratio taken by a simple tape measure may be the more accurate indicator at assessing heart-disease risk.

"Given that so many people are overweight and obese, we really have to figure out ways to determine which obese individuals are most at risk for heart disease," Dr. de Lemos said. "We discovered that taking out a tape measure and determining their waist-to-hip ratio is one accurate way to know who we should focus on."

Their research found that calcium was more likely to be found in the arteries of people with the greatest waist-to-hip ratio, even at small increments of widening waists.

"We discovered that the mirror may be more important than the scale in determining risk for heart disease," he said. "The more round or apple-shaped you are, the higher the risk for atherosclerosis. People need to prevent accumulation of central fat, or the 'pot belly,' early on in their lives."

While correct information can motivate people to change the things they can control to decrease their heart disease risk, UT Southwestern doctors know some people may need

something tangible, physiological, before they believe heart disease is a personal threat to them and something they should take action to prevent.

UT Southwestern practicing cardiologists are at the forefront of creating blood-based tests, or biomarkers, to predict heart disease risk. These tests would measure specific proteins found in the blood. Dr. de Lemos is a national



Dr. James de Lemos

expert on such biomarkers, and he and his colleagues have identified more than 100 proteins that together could more accurately and effectively assess individual heart disease risk in people who have shown no other symptoms.

His focused research of cardiac troponin T, for example, found that people with detectable levels were seven times more likely to die from heart disease within six years.

"This test is among the most powerful predictors of death in the general population that we've seen so far," he said. "It appears the higher your troponin T, the more likely you are to have problems with your heart, and the worse you're going to do, regardless of your other risk factors."

Another physiological screening vetted by UT Southwestern doctors involves the use of computed tomography (CT) scans. Dr. de Lemos and colleagues tested a recommendation by a national heart attack prevention society about whether use of CT scans for calcium deposits and blockages could identify people at risk for heart disease and who could benefit from cholesterol-lowering therapy. Their research found that the additional imaging

did indeed increase the number of patients classified into higher-risk categories.

"We found a 27 percent relative increase in the proportion of patients who would need cholesterol-lowering therapy," Dr. de Lemos said. "That would equal about one in every seven people who had calcium imaging needing to readjust their cholesterol goals to lower levels to prevent future heart attacks and strokes."

These researchers carry the knowledge from their studies of these scans into the clinic to determine who would most benefit from the scans and what to do with the results. Preventive cardiologists at UT Southwestern commonly perform these calcium scans in patients who may be at higher risk for heart attacks than their risk factors suggest, including those with a strong family history, to help determine if they will benefit from cholesterol-lowering and other medications. "In other patients with borderline risk factors, the absence of any calcium carries a good prognosis and can mean avoiding medicines altogether," Dr. Khera said.

Heart Study proves universal

All of this research has come from the Dallas Heart Study, a groundbreaking clinical investigation begun in 2000. UT Southwestern was selected over other top-tier, elite institutions to receive funding from the Donald W. Reynolds Foundation for the multimilliondollar project.

The study, a population-based study to discover the hidden cause of heart disease, first involved more than 6,100 Dallas County residents. More than 3,500 participants provided blood samples and underwent multiple body scans with magnetic resonance imaging and CT to examine the heart and other organs. Researchers at UT Southwestern then tracked the cause and time of death of participants, ages 30 to 65, through 2007.

The study's design is particularly unique. It's comprehensive enough to answer almost any question about heart disease that scientists can think to ask. And it's especially relevant to America's urban settings. African Americans were over-sampled during participant recruitment so that they comprise 50 percent of the study population.

Colby Ayers, faculty associate at UT Southwestern, chief statistician for the Dallas Heart Study and statistical adviser to the department



Dallas County residents participated in the Dallas Heart Study, launched in 2000 to discover hidden causes of cardiovascular disease.

of cardiology, said the multiyear investigation mirrors the populations of most U.S. cities. "One of the many strengths of the Dallas Heart Study is that important findings can be used at the community level."

While the study's findings will be a source of scientific information for many years to come, UT Southwestern cardiologists also are exploring other avenues to reduce health risks. One of the more intriguing is the interplay between exercise and heart disease.

Most people have heard and accept that if they exercise they might be able to stave off diabetes, obesity and heart disease for a while. Moving beyond these general benefits, UT Southwestern researchers, in conjunction with the Cooper Institute of Dallas, have found that the level and intensity of exercise a person can do on a treadmill may actually tell how likely they are to die decades later from heart disease.

Researchers analyzed the heart disease risk of 45-, 55- and 65-year-old men based on their fitness level and traditional risk factors – age, systolic blood pressure, diabetes, total cholesterol and smoking habits – and found that low levels of midlife fitness, measured by how fast and long someone could exercise, are associated with marked differences in lifetime risk for cardiovascular disease. Higher fitness levels lowered the lifetime risk of heart disease even in people with other risk factors.

Researchers also found the same treadmill test predicts how likely a person is to die of heart disease or stroke more accurately than assessing the risk using only traditional prediction tools.

For this work, the American Heart Association (AHA) gave the Elizabeth Barrett-Connor Research Award in Epidemiology to Dr. Sachin Gupta, postdoctoral trainee in internal medicine. The award is one of the AHA's most prestigious awards, recognizing excellence in research by an early-career investigator.

"Our study shows that fitness level measured in middle age can significantly improve risk prediction algorithms and help to identify individuals at risk for cardiovascular death both in the short term and in the long term." Dr. Gupta said.

This trial has great potential for everyone but special significance for youth and women, who have fewer prediction tools to assess long-term cardiovascular risk.

"Nearly all women in the U.S. less than 50 years of age are at low risk for heart disease," said Dr. Berry, a Dedman Family Scholar in Clinical Care. "As women get older, however, their risk increases dramatically. In our study, we found that low levels of fitness were particularly helpful in identifying women at risk for heart disease over the long term."

UT Southwestern, Cooper partner

These studies were done in conjunction with the Cooper Institute, which has compiled data on exercise and fitness from healthy volunteers for 40 years. UT Southwestern has a partnership with the institute, the preventive medicine research and educational nonprofit located at the Cooper Aerobics Center, to develop a joint scientific medical research program aimed at improving health and preventing a wide range of chronic diseases.

Drs. Jarett Berry, Sachin Gupta



The hallmark study from the institute – the Cooper Center Longitudinal Study – includes detailed information from more than 250,000 clinic visits that has been collected since Dr. Kenneth Cooper founded the institute and clinic in 1970.

Large population studies like Dallas Heart and Cooper Center Longitudinal allow researchers to examine not only factors contributing to disease but, more importantly, factors that promote cardiovascular health.

"We're as interested in the protective factors as the harmful ones," Dr. de Lemos said. "For example, we are going to learn a huge amount from people who live their whole lives overweight or obese yet never develop cardiovascular complications - we've found a lot of people like that in our study."

Doctors now are bringing these tests for silent signals of heart disease to fruition and seeing how they work in the real world. For example, UT Southwestern researchers have found differences in blood levels of C-reactive protein (CRP) according to race or sex. CRP is a marker of inflammation and has been heavily touted as a test to improve prediction of heart attacks.

"White woman have higher levels of CRP than both black and white men," Dr. Khera said. "Since white women have lower rates of cardiovascular disease, this study raises some question about how to best use CRP in the real world."

Dr. Khera said some tests may call for different thresholds between men and women to determine more accurately the risk of heart disease, and that overreliance on CRP for risk assessment in African-American patients may overestimate risk for cardiac and vascular events, since more than one-half of these patients had elevated levels.

Some of these signals are stronger for certain types of heart disease: calcium scanning for increased risk of heart attack, fitness level and cardiac troponin T detection for heart failure.

"We believe that combining imaging tests with protein tests is going to help identify people who feel perfectly well but who will have notably increased risk of heart complications down the line," Dr. de Lemos said.

The findings about fitness are now available and can be accessed at www.lifetimerisk.org. On this website, an individual can help determine his or her lifetime risk for cardiovascular disease by entering their age, sex, fitness level and other risk information.

"Without clear guidance and accepted algorithms for test interpretation, there is potential for both inappropriate under-treatment and over-treatment of individuals based on test results," Dr. Khera said. "Still, we think critically and carefully about how to help identify those people who seem healthy, but are at increased risk of heart disease later on." As long as heart disease remains rampant, UT Southwestern researchers will work to prevent it, tweaking traditional prediction tools and creating new ones as a preemptive strike against heart disease to eliminate sneak attacks in people without obvious symptoms of disease.

Even though heart disease is the leading cause of death in the U.S., its incidence is declining in large segments of the general population due to decreases in cigarette smoking and improved cholesterol levels. The nation's aging population and its rising obesity epidemic, however, run counter to health-conscious gains.

"Every adult in America is potentially at risk for heart disease in some form or fashion. Once you have a heart attack, the risk for additional heart problems down the road is much higher," said Dr. Khera, co-chair of the American Heart Association's state advocacy committee. "We're proud that we're doing the work on the front end to make sure the horse never leaves the barn."

Increased screening is one solution, but even then, approved implementation will be challenging.



"Fitness has the potential to have a large impact because everybody can do it," Dr. Khera said. "Fitness is relatively easy to measure, costs very little to improve, and people want alternatives to medicines."

Cardio health balance delicate

"We've learned a lot already about discovering the silent signals of the heart," Dr. de Lemos said, "and have great hope that bigger things will come."



Brave New World: Fightech Medicine UT Southwestern innovates with many different technologies to advance medical discovery and revolutionize patient care

By Debbie Bolles

he spiderlike robotic arms of a 1,200-pound machine slide into David Perdue's throat in search of their target – a pea-sized tumor inside his tongue, hidden from the human eye. Within two hours, the tumor and its cancerous tendrils extending to adjacent muscles are skillfully removed by the da Vinci surgical system, as the patient's doctor sits 5 feet away.

Science fiction? Not at all. Today, medicine and technology are merging at UT Southwestern Medical Center to improve patient care and advance scientific discovery.

Whether it's robotically assisted surgery, radiation therapy delivered by leading-edge machinery like the Vero – one of only three in the world and designed to locate tumors and direct precise radiation where needed – or imaging devices that use injected contrast agents to track a disease's metabolic changes, high tech medicine has shifted from the realm of futuristic storytelling to the new reality of care.

"Through technology, doctors are learning and finding new and better ways to do everything they do," said Mr. Perdue, now cancer-free after his robotically assisted operation in January 2011. After watching videos of the da Vinci machine online and discussing the procedure with his surgeon, Dr. Baran Sumer, assistant professor of otolaryngology – head and neck surgery, Mr. Perdue said his initial qualms about being operated on by a machine, controlled remotely by Dr. Sumer, faded fast.

At least a dozen UT Southwestern surgeons in a variety of specialties now use the da Vinci system. Dr. Claus Roehrborn, chairman of urology, was one of the earliest adopters on campus.



"The da Vinci system does not work autonomously, instead, it translates the surgeon's hand motions from a console nearby."

- Dr. Claus Roehrborn

"We were all skeptical at first," said Dr. Roehrborn, who has completed nearly 900 robotically assisted surgeries. "I couldn't possibly conceive of this as being as good as open surgery, but now looking back, I can see it the other way around. In the end, it's a device, and what matters is the surgeon behind the device."

Fast-forward 50 years and Dr. Kemp Kernstine, chairman of the division of thoracic surgery, says he wouldn't be surprised to see microscopic machines injected into people to perform surgical tasks.

"They could conceivably inject equipment into a patient's belly, then the machine assembles itself and the crawler finds the appendix, cuts it out and sews the surgical hole. With the next bowel movement, the appendix and all equipment are passed," said Dr. Kernstine of a hypothetical, yet very possible, scenario.

In the end, though, the success of any such procedure falls back on a medical professional's skill at using technology to perform tasks more quickly, efficiently or precisely, or less invasively.

Virtual reality

Centuries before the word "robot" was coined, Greek poet Homer and artist Leonardo da Vinci imagined machines with human-like intelligence. Their visions weren't just fantasy. In the 1950s, inventors built the first robots, which evolved by the 1980s into surgical applications.

Minimally invasive laparoscopic surgery began in 1987, with shortcomings of this technology leading to development of the first robotically assisted surgical tools. Subsequently, officials of the U.S. Army had an epiphany: create a robot that could be sent to the battlefield to treat wounded soldiers. Reality didn't quite coincide with the vision, however, since such a system still required a person assisting at the scene, even though a surgeon could operate the robot by remote control.

"If the hope was to make the surgery independent of the surgeon, ironically it is almost the opposite," said Dr. Roehrborn, who holds the E.E. Fogelson and Greer Garson Fogelson Distinguished Chair in Urology and the S.T. Harris Family Chair in Medical Science, in Honor of John D. McConnell, M.D. The da Vinci system does not work autonomously, Dr. Roehrborn explained. Instead, it translates the surgeon's hand motions from a console nearby, similar to a virtual reality game. The surgeon uses a viewer to operate the robot's three tool arms and camera from this same console.

In the aftermath of the failed Army experiment, Intuitive Surgical Inc. further developed and tested surgical robotics. In 2000, its da Vinci



system received Food and Drug Administration approval. UT Southwestern bought its first da Vinci system in 2006, and since has added three more.

Dr. Roehrborn uses the da Vinci for about 98 percent of the prostatectomies he performs. The system works well for targeted organ or tissue resections, including cancer removal, he said. UT Southwestern urologists, gynecologists and surgeons specializing in abdominal, colon, pancreatic, esophagus, thymus and lung cancer removal also use robotically assisted surgery. In cases where surgery is not done through a body opening, the device makes up to four small incisions, or ports, in the body for access.

"The surgery takes about the same time, but there's much less pain for the patient. There also is less bleeding, hospital stays are shorter and recovery time is much faster," said Dr. Roehrborn of robotic surgery.

Dr. Kernstine, who recently joined UT Southwestern, was one of the first surgeons nationally to use the da Vinci system for lung, thymic and esophageal cancer removal. The holder of the Robert Tucker Hayes Foundation Distinguished Chair in Cardiothoracic Surgery estimated that he's performed more than 400 robotic surgeries since 2002, including recent ones at UT Southwestern. Amazingly, a cancerous lung lobe about the size of a small loaf of bread can be bagged by the robot and pulled out through an incision no longer than 4 centimeters. That compares to a potentially foot-long or longer incision for the same procedure using conventional surgery. "About half of my patients are going home on minimal pain medication, if any at all, because we're really not causing much trauma to the chest wall since the robot is bypassing the nerves," Dr. Kernstine said.

to the chest wall since the robot is bypassing the nerves," Dr. Kernstine said. In the future, improvements to the robotic system will mean even less invasive surgeries for patients. Dr. Sumer said a new da Vinci prototype requires only one port for entry of the robot's arms, rather than up to three. "It's pretty wild. The arms go straight in and then flare out inside the body," he said.

Sc

Technology also extends into imaging and the detection and treatment of disease. The slow-growing brain tumor causing dozens of seizures a day and worsening leg weakness for 25-year-old Thomas Smith looked the same month after month on a magnetic resonance imaging (MRI) scan. Was his weakness from the tumor or seizures? The MRI wasn't helping to guide a decision about the optimal time to start chemotherapy.

Scoping out disease

Dr. Kemp Kernstine operates using the da Vinci surgical system, a robotically assisted tool that he has been using for lung, thymic and esophageal cancer removal since 2002.



Using advanced technology, such as this recently installed positron emission mammography (PEM) device used for breast cancer detection, Dr. Robert Lenkinski plans to test new imaging agents that will provide more detailed disease information.

By modifying the settings of the magnet during an MRI scan, Dr. Changho Choi, associate professor of radiology in the Advanced Imaging Research Center (AIRC), enhanced the magnetic resonance spectroscopy and identified a protein that accumulates in the tumor cells of patients such as Mr. Smith with a specific genetic mutation. When Mr. Smith's symptoms worsened, his doctors noted huge spikes of this protein showing up on a research study scan. They have since treated the tumor and the levels of this protein have fallen. Mr. Smith now walks without difficulty and his seizures are gone.

"This marks the first time a mutational biomarker has been identified through imaging," said Dr. Elizabeth Maher, associate professor of internal medicine and neurology and neurotherapeutics, and the lead investigator in this clinical trial. "It is a major breakthrough in

our ability to treat patients." Dr. Maher holds the Theodore H. Strauss Professorship in Neuro-Oncology.

UT Southwestern researchers and clinicians daily are using new imaging technology to improve diagnosis and treatment, often probing disease processes at the molecular level. Other imaging innovations at the medical center include more precise and less invasive imaging tools, development of contrast agents that literally "light up" disease processes never before seen and application of imaging devices for nonsurgical treatments.

Dr. Neil Rofsky, chairman of radiology, expects imaging technologies to become more pervasive in medical procedures and diagnostic tests as advancements continue.

"We'll be able to visualize processes at a level previously impossible and be able to use that information in real time to make decisions about therapies that may optimize efficacies for patients," said Dr. Rofsky, who holds the Effie and Wofford Cain Distinguished Chair in Diagnostic Imaging.

One example of this type of microscopic detail involves how researchers at the AIRC are developing hyperpolarized solutions for use in MRIs. Pyruvate, a naturally occurring metabolite, or small molecule, can be manipulated to increase its sensitivity to MR signals, including when it metabolizes into lactate. Lactate is produced during cellular respiration as glucose breaks down.

"It's a complicated method for increasing the MR signal of specific molecules in metabolic pathways. You inject those, and you can see a signal you otherwise would not see," said Dr. Robert Lenkinski, professor and vice chairman of research in radiology, who is testing hyperpolarized agents, along with Dr. Dean Sherry, professor of radiology and director of the AIRC, and Dr. Craig Malloy, professor of internal medicine and radiology in the AIRC and holder of the Richard A. Lange Chair in Cardiology.

After injecting hyperpolarized pyruvate into the body intravenously, doctors can potentially see how much of a person's heart muscle is metabolizing well, based on the MR image of pyruvate's changes.

"You can tell which part of the heart is doing well and which is not. That will help in designing an intervention or drug, or assessing if a treatment is working," said Dr. Lenkinski.

In similar research but using different technology, Dr. Sumer, the robotic surgery expert for head and neck cancer removal, is working with Dr. Jinming Gao, professor of pharmacology in the Harold C. Simmons Comprehensive Cancer Center, to develop nanotechnologybased fluorescent contrast agents for MR cancer imaging. Using imaging agents, the researchers have developed injectable pH-sensitive nanoparticles that light up with fluorescence in the low-pH tumor environment. Because most solid cancers are slightly acidic, this off-to-on mechanism fluorescently identifies the tumor's borders, allowing the surgeon to remove the cancer more accurately.

The research team also is creating nanoparticles with targeting proteins on their surface that will direct the nanoprobes to blood vessels feeding a tumor, stromal cells around the tumor, and the cancer cells themselves.

Still to come, another research team will develop tracers for positron emission tomography (PET) used in cancer diagnosis and



mammography (PEM) unit was installed at the Mary Nell and Ralph B. Rogers Magnetic Resonance Imaging Center on the North Campus. This technology helps pinpoint cancer in women with dense breast tissue and shows tumor characteristic detail.

Imaging technology also has expanded to novel treatment methods. A new type of ultrasound uses the heat of high-intensity focused ultrasound (HIFU) waves for noninvasive surgery, such as uterine fibroid removal. UT Southwestern researchers also plan to test MR-guided HIFU for prostate cancer treatment. "A tremendous amount of energy is deposited in a very tiny spot. We irradiate with ultrasound," Dr. Rofsky said.

As associate professor of health studies at Texas Woman's University, Dr. Kristin Wiginton is quite knowledgeable regarding the latest medical technology. She never imagined, however, becoming a pioneer in testing a new radiation treatment for breast cancer.

After being diagnosed, Dr. Wiginton faced a difficult decision. Because heart disease runs in her family, she knew that traditional radiation

treatment. Dr. Xiankai Sun, assistant professor of radiology, plans to use funds from a Cancer Prevention and Research Institute of Texas grant to purchase a biomedical cyclotron, a machine that produces radioisotopes for production of PET tracers. Medical institutions or research centers that have their own cyclotrons can produce a variety of PET tracers on-site for immediate use.

Taking advantage of new imaging technology remains a priority at UT Southwestern. In October 2011, the first positron emission

"This marks the first time a mutational biomarker has been identified through imaging."

- Dr. Elizabeth Maher

Revolutionizing radiation therapy

therapy potentially could damage her heart. So she took a risk, becoming the first woman to participate in a clinical trial at UT Southwestern using precisely focused high-beam radiation to treat breast cancer. After five radiation treatments in 2011, the results are encouraging. The study still is under way.

"I feel I made the right decision volunteering for this clinical trial," said Dr. Wiginton. "All in all, I think my recovery and comfort levels have been much better than if I had gone through traditional whole-breast radiation."

This first trial in the region using the Accuray CyberKnife System not only cut treatment time by 83 percent for Dr. Wiginton and other trial



"We are the pioneers in advanced technology in radiation oncology, but there is a fine line between curing cancer and preserving quality of life."

-Dr. Hak Choy

participants, it also illustrates the real results of cutting-edge research into new radiation therapies and technologies embraced by UT Southwestern.

"We are the pioneers in advanced technology in radiation oncology, but there is a fine line between curing cancer and preserving quality of life," said Dr. Hak Choy, chairman of radiation oncology and holder of the Nancy B. and Jake L. Hamon Distinguished Chair in Therapeutic Oncology Research.

The balancing act means killing as much cancer as possible with radiation while minimizing harm to healthy tissue. It's a challenge that UT Southwestern radiation oncologists face and make advancements in constantly.

The stars in UT Southwestern's radiation oncology arsenal include the Gamma Knife Perfexion system, which effectively treats multiple tumors in the brain, the CyberKnife high-beam radiation system and the Vero, a machine that directs radiation precisely where needed through stereotactic body radiation therapy, or SBRT.

Without the human element, however, such machinery would be useless. Some of the most renowned radiation oncology experts in the country conduct breakthrough research at UT Southwestern, including Dr. Robert Timmerman, vice chairman of radiation oncology and professor of neurological surgery. Dr. Timmerman, one of the nation's top experts on SBRT, led the CyberKnife breast cancer trial and currently is co-leading a multi-institutional study comparing the effectiveness of minimally invasive surgery versus SBRT in 400 non-small cell lung cancer patients.

"In the past, patients have been offered limited treatment options for this highly deadly disease," said Dr. Timmerman, holder of the Effie Marie Cain Distinguished Chair in Cancer Therapy Research. "This trial will show us how best to deploy both therapies and optimize them for a given patient."

In a related study, Dr. Timmerman also is testing hypofractionated image-guided radiotherapy on non-small cell lung cancer patients. This type of treatment uses advanced imaging, motion control and dosimetry principles to deliver treatments at higher doses, and with more precision. These methods include monitoring movement of lung cancer tumors through imaging techniques as a patient breathes and then adjusting radiation beams accordingly.

Since most tumors are closely situated within normal tissues, potent radiation can be a double-edged sword. With these and other advances, however, radiation therapy is becoming faster, safer and more precise, as well as less recovery-intensive for patients.

A picture in Dr. Choy's office of a radiation therapy machine used to treat a boy for ringworm at an Italian hospital in 1903 is a stark reminder of just how far this technology has evolved. In his 20-plus years as a radiation oncologist, Dr. Choy has seen significant advancements – such as radiation treatments evolving from inpatient to outpatient procedures.

"We are truly the most sophisticated center for radiation therapy. Our patients come from all over the world seeking the best technology and the experts in the field," Dr. Choy said.

For his part, Mr. Perdue says he's an ideal example and an avid proponent of the benefits of such high tech medical delivery.

"There are so many new and better ways to do things. We, as patients, need to be open to those new findings and techniques," he said. "If we're not, I think we're missing the boat and making a grave mistake."

Researchers develop effective radiation protocol with fewer treatments | by Robin Russell

Your doctor diagnoses you with prostate cancer, and your mind reels. You are scared, worry about loss of sexual function and maybe don't even want to discuss it.

Men diagnosed with low-risk prostate cancer currently must consider several treatment options – active surveillance, radiation therapy, surgical removal of the gland – for this typically slow-growing disease. For those who choose radiation therapy, treatments for localized prostate cancer typically take 42 to 45 days, spanning eight to nine weeks.

Thanks to UT Southwestern Medical Center researchers using the latest technologies in a series of clinical trials, however, new protocols are being discovered.

In a recent multicenter trial, researchers tweaked increasingly higher doses of ultra-precise radiation known as stereotactic body radiation therapy (SBRT), and found it safe and effective for patients with low- to intermediate-risk prostate cancer, with fewer treatments needed.

The linchpin of UT Southwestern's SBRT program is the Vero. Installed in 2011, it is the only one in North America. The system – which initially is being used to treat patients with prostate and lung cancer – combines three different imaging technologies with a gimbaled X-ray delivery head, allowing physicians to follow and treat a moving target safely.

"The Vero gives us the most precise linear accelerator that can spare normal tissue while taking care of cancer," said Dr. Hak Choy, chairman of radiation oncology.

Trial researchers used SBRT to treat patients with localized prostate cancer in just five 30-minute sessions every other day, over the course of two weeks.

the urethra, the bladder or the rectum," said Dr. Robert Timmerman, vice chairman of radiation oncology and professor of neurological surgery.

Prostate cancer is the most common cancer in men, with some 230,000 cases diagnosed annually in the U.S. About half of those who are treated undergo radiation therapy. Not everyone is cured, however, because some tumors are resistant to radiation.

SBRT has been used effectively for patients with lung, liver and brain cancers. The UT Southwestern study tested whether high-potency treatments could work in a moving target like the prostate, which shifts considerably due to normal bladder and bowel functioning.

To avoid injuring healthy tissue, researchers used beams of radiation that were only millimeters larger than the target itself. That narrow scope helped avert consequences such as rectal injury, impotence and difficulty urinating.

The second phase of the clinical trial, completed in fall 2010, increased the dosage in participants by 10 percent. More than 90 percent of the 50 patients involved tolerated the therapy well. Following clinical trials, UT Southwestern researchers will work with a multicenter consortium to develop a next-step protocol to further improve the therapy.



"We were trying to develop a fast, convenient, outpatient, non-invasive treatment without injuring

Dr. Robert Timmerman talks with radiation therapist Lindsay Henry about the Vero, the latest imaging technology in UT Southwestern's arsenal of stereotactic body radiation therapy

MOMENTS DISCOFVERY

By Dr. Bruce A. Beutler, as told to Deborah Wormser

In 1993, Dr. Bruce Beutler – one of UT Southwestern Medical Center's first Howard Hughes Medical Institute (HHMI) investigators – embarked on a five-year journey that led to his discovery of how the innate immune system recognizes and responds to infection in mammals, an achievement that earned him the 2011 Nobel Prize in Physiology or Medicine. Dr. Beutler recently returned to UT Southwestern as director of the new Center for the Genetics of Host Defense and holder of the Raymond and Ellen Willie Distinguished Chair in Cancer Research, in Honor of Laverne and Raymond Willie Sr. Here, he describes the painstaking work that led to his discovery and the pressures bearing down upon him in the summer of 1998.



"My father encouraged me to go to medical school. And I am glad that he did."

My interest in science was sparked at an early age. When I was quite young I was interested in nature, especially animals, and kept lists of birds I had seen. I still go birding when I have a chance. I think the first spark of interest in science had to do with the aesthetic pleasure of nature. One day, my father (scientist Dr. Ernest Beutler) suggested that what I was doing was observation rather than science. He explained that science meant asking specific questions and addressing them through experimentation in order to gain insight into how things work.

My father was a distinguished biomedical researcher, a member of the National Academy of Sciences and winner of many awards. When I was about 14, I began working in his laboratory at the City of Hope Medical Center in Duarte, Calif. There I learned a great deal about how to purify proteins and analyze them, and also a fair amount about genetics. I loved lab work and devoted myself to it as much as I could.

I graduated early from high school and had a lot of advanced placement credit when, at 16, I went to college at the University of California, San Diego (UCSD), so I finished in two years. I certainly learned a lot about basic science, including genetics, at UCSD. But I was in a great hurry and actually looked on college, with its many humanities requirements, as an impediment to becoming an independent researcher.

I first learned about endotoxin, also known as lipopolysaccharide (LPS), from UCSD professor Dr. Abraham Braude [associate professor of internal medicine from 1953 to 1957 at what was then Southwestern Medical School of the University of Texas]. Later, understanding LPS formed the core of my research, but at that time it was iust a casual introduction. I didn't see it in its full context in those days. I saw it more as a laboratory

1964

At the age of 14, Bruce Beutler begins working in his father's laboratory at the City of Hope Medical Center in Duarte, Calif.

curiosity and didn't know how important it was in immunity and in disease.

My father encouraged me to go to medical school, and I am glad that he did. At the University of Chicago School of Medicine, I learned about the principal

challenges in biomedicine, which tend to change quite slowly over time. I was one of those people who went to medical school to learn about the pathogenesis of disease and to understand what the big questions were.

I first came to UT Southwestern in 1981 when I was matched to the house staff training program (internship). UT Southwestern was my first choice because I knew that I would get outstanding training here. And I did. Dr. Donald Seldin was one of my teachers, along with Dr. Daniel Foster, Dr. Jean Wilson and other greats of medicine and biomedical science. I spent a year as an internal medicine intern, and then a year as a neurology resident. The neurology program was run by Dr. Roger Rosenberg, who had made a strong pitch to recruit me.

1972



Infection connection

During my clinical training, I saw what a problem infection could be. Remember, I had learned something about LPS – endotoxin – from Dr. Braude and I began to think about it quite a lot in clinical terms, and to take note of the damage it could do. LPS is released from Gram-negative bacteria, sometimes even more after antibiotic therapy has begun than beforehand, and it causes fever, shock, abnormalities of blood coagulation and organ injury. This process is usually what kills, not the infection. I began to wonder why that was.

Did the bacteria utilize LPS as a virulence factor? Or was it simply a structural element, and in that case, was it the host reaction that was excessive? And why would excessive reactivity be retained in the course of evolution? At that point, it hadn't really occurred to me to address the question.

After two years of residency, I went to Rockefeller University, where my work demonstrated that tumor necrosis factor (TNF), an inflammatory protein the body produces in response to pathogens, is an extremely important effector protein of the innate immune system. It plays a part both in inflammation and in resisting infection. And it turned out to be an excellent therapeutic target: TNF blockade is now a standard way of treating many inflammatory diseases.

I returned to UT Southwestern in 1986 as an assistant professor.

With the passage of time, I realized that the key question about innate immune responses, especially where infection was concerned but perhaps more generally too, was "how is everything started?"

How is it that LPS activates the macrophage, which then makes TNF? What's the receptor for LPS? And how do we become aware of an infection during the first minutes or hours after we encounter microbes? In reality, these are all variants of the same question.

Our work was fairly fruitless from 1988 to 1992 because of the way we went about it. We tried to use classical immunological methods to find the difference between certain mice

1974

First learns about endotoxin, also known as lipopolysaccharide (LPS) Graduates from UCSD with bachelor's of arts, biology, at the age of 18 Enrolls in the University of California, San Diego, at the age of 16 1976





Dr. Beutler's father transforms his son's fascination with nature into a quest for knowledge

that couldn't respond to LPS and other mice that could. We also used analytical biochemistry and we used expression cDNA cloning. None of these methods led anywhere.

Applying genetics

The real epiphany for me was embracing classical genetics, starting in 1993, to try to solve the problem. And that was not accidental. I don't think I would have done it just anywhere. Genetics was so much a part of life here at UT Southwestern, and it was also a place where one could quickly learn about what everyone else was doing. The students in my lab would talk to students in other labs; there were really no barriers. And they would come back and chat with me about the latest innovations and about how to get things done.



There were three somewhat overlapping phases to our work: genetic mapping, physical mapping and gene identification.

In the first phase, we had to localize the mutation to a point between two markers on the chromosome. This involved a lot of breeding of mice, and analysis of whether they would respond to LPS.

In the second phase, we had to clone all the DNA between those two markers - about 2.6 million base pairs as we

originally estimated. This involved isolating huge pieces of DNA in bacterial artificial chromosomes (BACs) and yeast artificial chromosomes (YACs).

And in the third phase, we had to discover the gene content of those BACs and YACs, then search for a mutation in each of the genes we found to find the change in the genome that caused resistance to LPS in the C3H/HeJ strain of mouse. One must remember that in those days, the entire genome of the mouse was *terra incognita*; there was not even an accurate estimate of the number of genes, let alone what they might be.

Each phase was tough but each in a different way. I think the last two phases were the hardest. We mostly identified genes by sequencing the DNA, and sequencing 2.6 million base pairs of DNA – about 0.1 percent of the genome – was a real grind in an academic lab. Not only that, but today we know the size was really about twice what we thought; about 5.2 million base pairs of DNA. It was an assembly line. Someone would isolate BAC clones using markers within the critical region. Someone else would shear BACs with ultrasound and make libraries of the DNA

fragments, cloning them into Escherichia coli

1981



Finishes an internship in internal medicine and started a residency in neurology (1982-1983)

(E. coli), and plating the libraries on agar. Yet another would pick colonies and inoculate broth to grow each colony in liquid culture, then prepare DNA for sequencing from cultures that had grown the day before. Someone else would sequence the purified DNA.

I myself spent much of my time analyzing the sequence, and writing computer scripts to facilitate this. I should mention that Drs. Alexander Poltorak and Irina Smirnova, my postdoctoral researchers at that time and now independent scientists at Tufts University, were the tireless heroes of this effort, and without them, we surely would not have found the mutation.

Sequencing in the earliest days was done with radioactive nucleotides. You'd get a ladder of bands on a gel and you'd expose it overnight to X-ray film and read off the base pairs the next day. Betsy Layton, my administrative assistant, would read and I would type or vice versa. We would read about 4,000 to 5,000 bases of DNA in a morning, and that would be about the limit a person could tolerate reading in one day. Your eyes would get tired. Today's methods can

1982

"There were three somewhat overlapping phases to our work: genetic mapping, physical mapping and aene identification."

deliver about 1 million base pairs per second, and certainly nothing of the kind we attempted will ever be done again.

We were reading sequence in this manner in 1993 and 1994. Then, using my own funds, I bought a used ABI 373XL sequencer. That allowed us to sequence about 40,000 base pairs per day if we ran the machine around the clock. And we decentralized our sequencing also, farming it out to numerous core laboratories.

Working around the clock

We worked most weekends, and we'd also work until late at night. We would look at the results of the Basic Local Alignment Search Tool (BLAST) searches from sequencing that had been done during the day. We would see if our genomic sequences had matches in an expressed sequence tag (EST) database. We used both dbEST (database of Expressed Sequence Tags), which was public, and we used the TIGR (The Institute for Genomic Research) database, which was proprietary.

Both of those were databases of complementary DNA (cDNA) sequences, meaning they represented the parts of the genome that were known to be expressed as messenger RNA. The idea was to look for genes that way. If you BLAST a genomic DNA sequence and it has an EST match, that part of the genome is expressed and is part of a gene (with certain caveats; nothing is absolutely certain).

Starts research career at Rockefeller University where he is lead author of the first study to demonstrate the inflammatory activity of tumor necrosis factor (TNF)

1983

We cloned that immense span of DNA because we thought our mutation of interest must be somewhere within it. We refer to such a span of DNA as the "critical region." The array of YACs and BACs that contain that part of the genome is called the "contig." Alexander, Irina and I spent most of two years analyzing the contig. Betsy worked in administration for the lab but also physically organized massive amounts of data, inoculated colonies, helped read the sequence files and helped with the BLAST searches.

We'd open 50 or 60 BLAST searches and have Once, out of the blue, I received a telephone So for a time I cut back, mainly by stop-

them going at the same time - all open on the toolbar of the computer. Sometimes we'd have a memory problem and everything would shut down, which was most frustrating. call from someone at the National Center for Biotechnology Information, where the BLAST servers were housed, and the caller told me, "You've been doing too many BLAST searches and you can't do that many anymore." ping the recursive searches of old sequences as frequently as I had been doing them. I also bought a Linux computer of my own to BLAST locally after a while. They don't complain about things like that these days. By the summer of 1998, we had finished sequencing almost the entire contig and I knew

we were running out of anything to sequence. It was as though you've explored 90 percent of a room looking for a lost cufflink and thoroughly covered the room and looked under everything and you've looked at practically everything except one sofa. And you know it has to be under there, or else it's going to be nowhere in the room at all. It was that kind of

1986

SOUTHWESTERN ME

First comes to

an intern

30

UT Southwestern as

Returns to UT Southwestern as an assistant professor and assistant investigator at the Howard Hughes Medical Institute



31



Has an epiphany began embracing classical genetics

"We knew we had opened a new window in immunology."

feeling: that we were running out of anything to sequence and the probability of finding the mutation was increasing with every BAC that we'd explore. Either that or we'd made a terrible mistake of some kind, and the mutation wasn't in the critical region at all.

And we had learned only in May 1998 that our HHMI funding was going to end in August 2000. This was very disappointing because we'd really worked so hard on this difficult project and that was what they had encouraged us to do, but they had run out of patience.

A powerful match

On Sept. 5, 1998, I was in my study at home at about 9:30 p.m. We were doing BLAST analysis of the BAC I17, and I suddenly saw a powerful match between one of our genomic sequences and an EST. Then I saw another match. Each was nearly perfect, and I was confident that this was not a pseudogene. Looking further, I saw that the target gene was known as *Toll-like* receptor 4 (Tlr4), named for its similarity to the Drosophila Toll gene. And I also saw strong homology to the interleukin-1 (IL-1) receptor, which I knew produced a strongly inflammatory signal. I knew, too, that the Toll family had leucine-rich repeats, as did CD14 – the one protein that was known to be involved in LPS signaling, though it was not the product of the LPS locus. All these facts were exciting. But of course, they didn't yet prove that *Tlr4* was the gene we were after.

I remember telephoning Alexander immediately, and later telephoning my father to tell him about it, too, because I felt almost sure that this was the gene, based on the fact that we had been nearly exhaustive in covering the critical region if nothing else. That very night, I designed

1993

primers to amplify the cDNA for *Tlr4*, and the next morning Alexander and I had them synthesized.

By evening, he had begun to amplify using preparations of cDNA from the mutant C3H/ HeJ strain and the control C3H/HeN strains of mice. It was a very long cDNA – more than 4,000 base pairs. We were very skilled at shotgun cloning, using ultrasound to break up a piece of DNA, by that time. We'd shatter the DNA with ultrasound and then we'd clone all the pieces into a sequencing vector that had primer sites so we could sequence in both directions. We decided to fragment the band and sequence it in depth; then align the reads with Phrap, an assembly program. We saw the sequence about a week later, but couldn't view it with consed, the definitive program for visualizing aligned sequence, until Sept. 15. That was the day we were certain we saw the mutation in C3H/HeJ mice for the very first time, and that was the second moment of excitement.

I think it was the most thrilling moment of my career. It occurred over in the Y building [Green Research Building]: the critical moment of finding the mutation that distinguished endotoxin unresponsive mice from the control mice. I remember going to the computer in the corner of our lab to look at it and then I'd walk away and do some work and then go back and look at it again and again. After five years of searching, you can hardly believe it when you've really found what you've been looking for, given the many frustrations and false starts. But, indeed, it was real. Still, there was one final piece of proof missing.

We knew of another strain of mice – C57BL/10ScCr – that also couldn't respond to LPS. And we were confident on genetic grounds



A powerful match is found, leading to confirmatory experiments, and the writing of a landmark paper published in *Science* that December

1998

2008

Is elected to the National Academy of Sciences and the Institute of Medicine

that they had a defect in the same gene. We looked at this second strain of mouse and we found we couldn't amplify the cDNA at all, nor any part of the gene. We did a Southern blot (a test to determine if a DNA sample contains a specific genetic sequence) to see if we could detect the gene by probing it on a nylon membrane, and we couldn't detect the gene that way either. It seemed that in the control strain, known as C57BL/10ScSn, the gene was there, but in the C57BL/10ScCr strain, the gene was gone. Eventually, by sequencing, we found that 74,000 base pairs of DNA were missing from the genome of this mouse. Only *Tlr4* was excised; no other genes were harmed.

That was really incontrovertible evidence. Here we had two different alleles: One was a point mutation, one was a large deletion. The first was likely to destroy *Tlr4*, and the second certainly did so. Both of them caused endotoxin resistance. We concluded that *Tlr4* must be necessary for the response to endotoxin.

Finding the C57BL/10ScCr mutation might have occurred perhaps a week later, no more than that, because we were quite confident that we had really found the relevant locus. By Sept. 30, 1998, we had submitted our paper to *Science*.

The paper was reviewed quite promptly, and there were only minor revisions to be made. It was published in December 1998. We knew we had opened a new window in immunology, discovering how the innate immune system "sees" microbes. And we had found the very molecule that initiates Gramnegative septic shock. Returns to UT Southwestern as Director of the new Center for the Genetics of Host Defense

Wins Shaw Prize in Life Science and Medicine

Is awarded the 2011 Nobel Prize in Physiology or Medicine

2011



The Hospital of the Future

Designed around the needs of patients and their families, the new UT Southwestern University Hospital will be as innovative as the scientific discoveries for which the medical center is known

- *U.S. News & World Report* has ranked UT Southwestern Medical Center as the top hospital in the Dallas-Fort Worth region, with six nationally recognized specialties.
- University Hospital Zale Lipshy was one of just three hospitals in the nation to earn the Patient Voice Award for Academic Medical Centers from Press Ganey, an independent firm that tracks patient safety and satisfaction.
- University Hospital St. Paul ranks No. 1 in Texas for survival rates for heart transplants and in the top 5 percent of programs in the country.
- University Hospitals & Clinics were named to the "Most Wired" list by *Hospitals & Health Networks*.

So, what's next?

by Russell Rian

Envisioning – and building – the hospital of the future.

Dr. Daniel K. Podolsky, president of UT Southwestern, laid out the challenge.

"After a careful assessment it became clear the aging University Hospital - St. Paul could not be economically upgraded to fully achieve our aspirations: to provide world-class patient care in a comprehensive, state-of-the-art academic medical center," said Dr. Podolsky, who holds the Philip O'Bryan Montgomery Jr., M.D., Distinguished Presidential Chair in Academic Administration and the Doris and Bryan Wildenthal Distinguished Chair in Medical Science.

This facility needed to be more than just a rebuild, he emphasized, and had to deliver beyond being just a showcase for UT Southwestern's expertise in clinical services like those recognized by U.S. News & World Report: urology, cardiology/heart surgery, diabetes/ endocrinology, gynecology, nephrology and

The call also went out to the medical center and the broader community for ideas and input. More than 800 people responded. Civic leaders. Patients. Doctors. Nurses. Technicians. Staffers. Students. Community members.

As work groups took up the challenge of what would be needed and how to arrange all the pieces cohesively and coherently, the process distilled to a single, rather simple question: How do we improve patient outcomes while integrating our other missions of research and education into a single new hospital?

To find the right answers, teams examined

"We really tried to test our own ideas," said

what worked and what didn't, then traveled

around the nation to see whether the ideas

Dr. John Warner, chief executive officer for

UT Southwestern Hospitals. "We tried to figure

out how to borrow from other places that have

done things really well and we tried to go to a

wide variety of hospitals, not just the top 10

academic medical centers." Dr. Warner holds

the Jim and Norma Smith Distinguished Chair

and Bernard Rapoport Chair in Cardiovascular

for Interventional Cardiology and the Audre

Research.

being considered worked elsewhere.

Dr. Daniel K. Podolsky

"We went to places that had the fastest turnaround for emergency patients, community hospitals that did it really well, to determine what they did, the way they organized themselves and the way they planned their space," Dr. Warner said.

In the end, the answer was rather simple:

"We want to take care of the person who has a disease, not just the disease itself," summarized Dr. Bruce Meyer, executive vice president for health system affairs and professor of obstetrics and gynecology.

The challenge: to turn competitive environments into complementary ones; to seamlessly blend practicality into practice; to deliver patient-room convenience by embracing tomorrow's technology; to transform visions into something visionary.

A patient-centered approach

"At every step along the way, we asked ourselves a key question: How can we make this better for patients?" explained Dr. Podolsky. "And it shows. This will be a different kind of hospital and you will see that from the moment you enter the lobby."

Four simple themes emerged from that initial question of how to make patients well, and they are woven into every aspect of the new building: safety, privacy, communication and flexibility.

Each harmonizes with the other. Safety depends on good communication and privacy. Privacy factors significantly into effective communication and safety. Flexibility is essential to good communication, privacy and safety.

While the scope of the project remained constant, the shape of the building evolved. What started as a traditional four-cornered building became a unique "W" shaped design so that nurses could be closer to patients, have a more direct view of beds and not have to disturb patients just to monitor them.

Every patient room in the new hospital is private. There's an obvious comfort factor in not having to listen to the person next to you cough or wheeze and in not being disturbed when someone else is being attended to. Privacy obviously averts the awkward moments at the hospital – bathing, asking your neighbor to turn down the television's volume or listening to others sharing their struggles with family and friends.



Each of the 460 patient rooms in the hospital will be private with accommodations for family to stay overnight or virtually visit by video-conference (pictured above). Patient rooms will feature comfortable seating areas for visitors, bedside and dimmer controls for lighting, multimedia options and Internet access.



Family comfort and privacy figure prominently into the design of two waiting areas located on each patient floor (pictured above). A frosted glass wall will shield the waiting room from elevators and a secluded cell phone area will provide a quiet space for private calls. The hospital also will include 16 labor and delivery suites (pictured below).



In addition to the personal benefits, privacy serves practical purposes, as an effective tool for reducing the spread of infections, both into and out of the room.

"We want everyone to have their own room since infection risks are much lower when patients have privacy," said Dr. Gary Reed, chief quality officer and professor of internal medicine. Dr. Reed holds the Sinor/Pritchard (Katy Sinor and Kay Pritchard) Professorship in Medical Education Honoring Donald W. Seldin, M.D.; the S.T. Harris Family Distinguished Chair in Internal Medicine; and the Eva A. Rosenthal Professorship in Internal Medicine.

The one patient/one room model also means that when caregivers are assembled, they are only focused on that patient's needs so there's less confusion, less bustle and less chance of error. It means only equipment needed for that patient's care needs to be in the room, so there's more space for family and friends. It means the sometimes embarrassing moments don't have to be shared, nor the sometimes painful ones. And it all happens in an environment where there is a better opportunity to communicate what both patients and their caregivers need to know to achieve positive outcomes.

A healing environment

Beyond merely embracing the medical advantages inherent in a new hospital, design teams also thought about home comforts. One essential element of feeling better is having some control of your surroundings and environment, so designers incorporated bedside and dimmer controls for lighting and temperature, multimedia options at patients' fingertips and Internet access for laptops, phones and other devices that they would otherwise be enjoying at home.

Another well-established critical comfort factor for patients is having friends and family there, so each room will feature a dedicated seating area for visitors, as well as a pull-out sofa bed so a spouse or other loved one can stay overnight. As is the case with home visitations, family and friends who come to visit patients at the new University Hospital will feel welcome and will be treated well. So each patient floor will include two family waiting areas that provide comfortable and private spaces for patients' visitors to gather. Each floor also will include family conference rooms for private consultations with physicians.

By The Numbers:

UT Southwestern's new University Hospital, scheduled to open in 2015, will have:

- 12 floors
- Approximately 1.3 million square feet of space
- 460 private patient rooms
- 72 private adult ICU rooms
- 30 private neonatal ICU rooms
- 16 labor and delivery suites
- 40 rooms in the emergency department complex

- 27 surgical suites
- 12 cardiac catheterization, electrophysiology, and interventional radiology procedure rooms
- 6 endoscopy rooms
- 4 CT scanning rooms
- 2 MRI rooms
- 4 X-ray suites

"My late wife spent a long time in various hospitals throughout the country," said Roger Horchow, founder of The Horchow Collection, Broadway producer, philanthropist and a member of the *Building the Future of Medicine* Campaign Steering Committee. "I know how difficult it can be to have a family member in the hospital, so it's critical that a hospital be designed to lessen a potentially stressful situation by providing a healing environment for patients and their families. The patient rooms will provide many of the comforts of home, which you don't often find in a hospital."

"The design is absolutely wonderful," said Gay Solomon, an interior designer who helped spearhead the public reviews for the new facility and whose husband, Bill Solomon, chairs the Campaign Steering Committee and serves as chairman of Southwestern Medical Foundation. "They've gone to elaborate measures to ensure plenty of community and patient-friendly input, as well as input from nurses and doctors, about what actually works. It's going to be an incredibly pleasant environment, very user friendly and relaxing, given the fact that people are going to be stressed when they are here."

The daily practicality of moving supplies - from sheets and towels to medications and monitors – is no small function at a major hospital and can add to that stressful environment. Recognizing this, designers took some lessons from production companies like Disney and four-star hotels to learn how to shift support operations backstage.

Pushing the operational side of things to the backstage by using separate elevators for patients, supplies and visitors or providing conference rooms for staff meetings and

briefings, addresses all the fundamentals – flexibility and privacy, safety and better communications – for both patients and employees.

The operational design focuses on frontline patient care, reducing distractions and facilitating better communications. Quieter, safer hallways translate to more privacy and a less crowded feel. Such operational considerations in the new University Hospital's design will ensure the patientcentered approach will continue, even when construction is complete.

Technology for family and care

With state-of-the-art medical technology, the new University Hospital will be as innovative as the health care at UT Southwestern. Each room will feature a monitor that allows patients and their caregivers to review charts and images, such as X-rays, CT scans and MRIs, facilitating better communication and privacy.

Notably, the monitor will also allow inroom video-conferencing, enabling patients to communicate virtually with members of their care team, out-of-office physicians, off-site primary care physicians, or family and friends. Such technology can help alleviate the solitude of treatment and recovery when a patient's loved ones are unable to visit in person.



patient-centric environment.

The new UT Southwestern University Hospital has been meticulously designed based on input from a dedicated planning team of physicians, nurses, institutional leaders and community supporters. Always mindful of the needs of patients and their families, the team envisioned a facility that will offer state-of-the-art, specialized care in a

The new University Hospital also will include an on-site education center, where patients or family members can find out more about diseases or treatments and get educational materials, including information about relevant research being done by UT Southwestern faculty.

Along those lines, the hospital will house and support clinical researchers who will work to translate scientific discoveries into treatments for patients. Yet another advantage of UT Southwestern's care is research – its mission to move laboratory findings to bedside practicality and improve clinical outcomes with trials of new drugs and other therapies. Funding from federal agencies, foundations, companies

and private donors provides more than \$417 million per year to support about 3,500 research

Enabling patients to take advantage of a clinical trial requires greater flexibility than is found at a typical hospital environment. So each floor of the new University Hospital will include dedicated research space for clinical and translational research activities, which can range from analyzing blood or tissue samples to entering data about the progression of a disease or illness and the progress in treating it.

Being able to handle research duties on-site means physicians can spend less time away from the hospital, making them more accessible to patients or other health care professionals.



A rendering of one of the hospital's three adult intensive care units (ICUs) is shown above.

Team-based care

UT Southwestern leadership takes pride in its team approach to health care – cardiologists work with cardiothoracic surgeons and anesthesiologists, specially trained teams of cardiac nurses join with technicians and imaging specialists, along with pathologists, case managers, social workers and therapists.

The medical center was among the first in the nation to use electronic health records. These records, used across the ambulatory and hospital environments, facilitate easier communication and help ensure patient safety by providing a seamless transfer of information among all members of a patient's care team. Every caregiver has the same information available when and where it's needed. The electronic system reduces the risk for error by requiring specific information, noting if a form hasn't been completed, informing care providers if there are problems with medication interactions, and other patient care safeguards.

"A lot of people talk about multidisciplinary care and team-based care, while in reality they are taking a team and moving it around the hospital," said Dr. Warner, associate professor of internal medicine who is also medical director of the Doris and Harry W. Bass Jr. Clinical Center for Heart, Lung and Vascular Disease. "This hospital will be built around team-based care. We thought about a process or a disease or a service and designed it so people who need to be working together will always be in close proximity to one another.

"In most hospitals, for example, a cardiac catheterization laboratory and the cardiovascular operating rooms are on different floors. Ours will be right next to each other. They're across the hall from each other, so everybody that has anything to do with the heart is on one floor."

A culture of communication

The team also may need to communicate immediately, so each of the hospital's surgical suites will be connected by live video to the pathology lab. This will enable surgeons and pathologists to view and discuss tissue specimens in real time while a procedure is still under way. The hospital plan includes on-call rooms and facilities for physicians, so they can access computers between surgeries or clinic visits without having to trek across campus. As part of the bigger picture, the new

into the hospital so that at every single step we added the ability to expand or renovate with minimal disruption to the building." Viewed from the perspective of Harry Hines Boulevard, the new University Hospital is an impressive construction site of an \$800 million facility. Institutionally, however, the project is being realized and fulfilled with each individual patient in mind, a perspective that is proving priceless. "As an academic medical center, chief among



An on-site education center (above) will provide patients and family members access to educational materials about diseases or treatments.

University Hospital will feature conference facilities as well, key to helping UT Southwestern's physicians stay atop the latest medical findings while meeting continuing education requirements and helping pass along the latest findings to other physicians in the community. "This facility will be one of the most adaptable hospitals in the country," said Dr. Warner. "We really tried to design flexibility

our missions is to translate whatever lessons we learn, from wherever we learn them, into something applicable to the bedside," Dr. Podolsky noted. "Our mission was to design the hospital of the future that would harmonize our clinical, educational and research missions at the bedside. It turned out to be quite a symphony."

Can Foodborne Illnesses be Stopped?

UT Southwestern researchers are at the forefront of understanding and preventing the spread of dangerous bacteria in food

You're looking for fresh produce at the grocery when a text comes across your smartphone. Holding the device away from your 3-year-old, you read a frantic message from your mother: "CANTALOUPES DANGEROUS!!! DO NOT BUY CANTALOUPES!!!" • Turns out the media are reporting a Listeria outbreak. In addition to her text message, your mother called five times. She's panicking because her grandchild, your toddler, happens to love cantaloupe. • The Centers for Disease Control and Prevention (CDC) estimates that each year foodborne illnesses sicken roughly one in six Americans, kill 3,000 and cause 128,000 to be hospitalized. The most commonly recognized bacterial pathogens are *Campylobacter jejuni* (*C. jejuni*), *Salmonella* and *Escherichia coli* (*E. coli*). • After contaminated food is consumed, the bacterium incubates in the host before revealing itself through illness symptoms. During incubation the bacterium passes through the stomach into the intestine, attaching itself to the cells lining the intestinal walls.

By Erin Prather Stafford



"Disease caused by foodborne pathogens can be anything from mild diarrhea in some individuals to more serious hemorrhagic diarrhea, kidney failure and strokelike symptoms. The bacteria can even be fatal, especially for young children, the elderly and those with compromised immune systems."

-Dr. Vanessa Sperandio

The pathogen then multiplies, killing cells by stealing their nutrients. Some of the bacteria stay in the intestine, while others produce toxins that then are absorbed into the host's bloodstream or even body tissues.

Many pathogens responsible for foodborne illness cause similar symptoms such as diarrhea, abdominal cramps and nausea. There is so much overlap that it can be difficult to identify what specific bacterium is causing illness without laboratory tests to identify the pathogen unless there is a recognized outbreak. Most cases are mild and can be treated by increasing fluid intake. But not all reactions are minor, and death is a tragic possibility. "These bacteria are very potent; it only takes a few to get someone severely sick," said Dr. Vanessa Sperandio, professor of microbiology and biochemistry at UT Southwestern Medical Center. "Disease caused by foodborne pathogens can be anything from mild diarrhea in some individuals to more serious hemorrhagic diarrhea, kidney failure and stroke-like symptoms. The bacteria can even be fatal, especially for young children, the elderly and those with compromised immune systems."

Many antibiotics have become ineffective against foodborne pathogens and can potentially cause more harm by increasing the amount of released toxins. Instead of focusing on the bugs after they cause illness, UT Southwestern researchers are investigating how to neutralize the pathogens so they never have a chance to wreak havoc on the human body.

Exploiting cell-to-cell signaling

Dr. Sperandio always has been fascinated with bacteria/host interactions. Much of her research has focused on *E. coli*, specifically the lethal enterohemorrhagic E. coli (EHEC) strain. The bacterium is primarily transmitted to humans through consumption of beef. However, fecal contamination of water and other foods, as well as cross contamination during food preparation, also can cause disease. Recent *E. coli* outbreaks have been linked to beef, cheese, cookie dough, poultry, Romaine lettuce, spinach and sprouts.

Dr. Sperandio and her team are investigating two tactics to fight the pathogen. The first involves exploiting its cell-to-cell signaling to stop EHEC from colonizing in the intestines. Her lab has successfully identified two receptors required by the bacteria for infection of the host.

In 2006 she found the receptor QseC, a protein in the EHEC's membrane. After a person ingests the bacterium, it travels peacefully through the digestive tract until reaching the intestine. Once there, the QseC receptor communicates with the human stress hormones epinephrine and norepinephrine, a signaling cascade begins and EHEC colonizes the intestine and causes disease.

Searching UT Southwestern's library of 150,000 small molecules, Dr. Sperandio uncovered LED209. Nontoxic to mammal cells, LED209 has proven successful in preventing QseC from initiating the virulence cascade and allowing EHEC to colonize.

She and research colleagues also are targeting EHEC in live cattle. An estimated 70 percent to 80 percent of herds in the U.S. carry the bacteria. Although deadly to humans, EHEC is a natural part of cattle's normal gastrointestinal flora. It harbors a gene called *SdiA*, which makes the *SdiA* protein. The *SdiA* protein senses a chemical made by microbes in the animal's rumen, the first of a cow's four stomachs, which serves as a large fermentation chamber. Detecting this signal allows EHEC to pass through the rumen and colonize the rectoanal junction.

Dr. Sperandio's lab injected two types of EHEC into the rumens of eight grain-fed adult cows. One mutant version lacked *SdiA* and could not detect the signal in the rumen. Another strain produced an enzyme that destroyed the chemicals in the rumen sensed by *SdiA*.

"If there's no signal, then there's no acid resistance, a requirement for the pathogen to make it to the recto-anal junction," Dr. tha in t find sys cat rea din una pro on

Dr. Sperandio said. "Everybody had thought that this type of signaling occurred naturally in the gastrointestinal tract of mammals. Our findings suggest we might be able to target this system to prevent food contamination from cattle. We can render EHEC harmless before it reaches humans."

Dr. Sperandio also found that colonization diminished significantly when EHEC was unable to sense the rumen chemicals. The process prevented the bacteria from moving on through the stomach and colonizing. Her next step is to assess what happens to cows fed a grass-based, rather than grain-based, diet.



E coli, shown forming lesions on host cells, is primarily transmitted to people by eating beef.

Stopping attachment

Bacterial pathogens face a number of challenges when trying to connect with human cells. Evading immune recognition, invading cell tissue and modulating cellular signaling are just a few tasks they must accomplish to ensure survival. Dr. Kim Orth, professor of molecular biology and biochemistry, is investigating whether cell damage caused by pathogens can be prevented by disrupting their initial attachment to host cells.

She and her team looked to the pathogen Vibrio parahaemolyticus (V. para) for answers. The bacterium, found in every ocean, can cause food poisoning through consumption of raw or undercooked shellfish, particularly oysters. Previous work by Dr. Orth had found that V. para kills its host's cells by causing them to burst, providing the bacteria with food used to fuel proliferation. To accomplish this nutrient robbery, the bacteria must successfully attach to the membranes of host cells.

"Bacteria are dependent on that union," said Dr. Orth, a W.W. Caruth Jr. Scholar in Medical Research. "We suspect many bacterial

"Bacteria have been evolving for a very long time. If we can figure out how they work, it could have an incredible impact on everyone in the world."

-Dr. Kim Orth



pathogens actually use a common mechanism to establish that first contact. Our goals are to understand this mechanism and then exploit it to develop therapeutic tools that completely shut down the pathogens' ability to colonize cells."

In investigating *V. para*, Dr. Orth's laboratory found that the protein MAM7 enables a wide range of pathogens (including *E. coli, Salmonella* and *Cholera*) to bind to host cells during the early stages of infection. When researchers deleted MAM7, *V. para* had difficulty binding to host cells and efficiently killing them.

They also engineered a harmless strain of *E. coli* to express MAM7. Exposing human cells to this harmless form of the bacteria caused human cells to become more resilient to *V. para* and other types of pathogenic bacteria. Dr. Orth is optimistic that the protein eventually could help prevent foodborne illness.

"It would be amazing to give susceptible children in pathogen-plagued areas a bit of yogurt containing some form of MAM7 and have it decrease their risk for serious complications," she said. "Bacteria have been evolving for a very long time. If we can figure out how they work, it could have an incredible impact on everyone in the world." "It's known that as people get older they become more susceptible to infectious diseases and also that autophagy decreases."

-Dr. Beth Levine

Autophagy fights back

Sometimes the answers to stopping bacterial pathogens are found in the cell's own natural process. Autophagy is the way cells eliminate their own unwanted or damaged parts. It is a highly regulated and completely normal process by which they remain healthy by performing "routine housekeeping" and "garbage disposal."

Dr. Beth Levine, director of the Center for Autophagy Research and professor of internal medicine and microbiology, has determined that autophagy prevents *Salmonella* bacteria from becoming successful intracellular pathogens. She and her team studied the effects of *Salmonella* infections in two organisms they had genetically engineered to lack active autophagy genes.

In both cases, the animals with inactive autophagy genes fared far worse than those with active ones. Rather than being targeted for elimination, the bacterium was able to invade the host cells, where it started replicating.

Dr. Levine's findings also suggest that decreases in autophagy – such as those that occur in the elderly and in certain patients with Crohn's disease – may lead to abnormalities in the way the intestinal tract deals with bacterial infections.

"It's known that as people get older they become more susceptible to infectious diseases and also that autophagy decreases," said Dr. Levine, who holds the Charles Cameron Sprague Distinguished Chair in Biomedical Science. "We've found that signaling pathways that extend life and protect against bacterial invaders do so by triggering autophagy. This suggests that therapeutic strategies to increase autophagy may be effective in defeating harmful bacteria that can enter inside cells."

It's unclear why older people become more susceptible to infections, but research has shown that autophagy declines with age. Dr. Levine, a Howard Hughes Medical Institute Investigator at UT Southwestern, suggests that by reversing or regulating this process, researchers could make the elderly and others with weakened immune systems more resistant to infections. Her lab is now looking into the efficacy of a new autophagy-inducing molecule for treating a number of intracellular bacterial infections including Salmonellosis, tuberculosis, tularemia and Listeriosis.



"Unlike in humans, C. jejuni does not invade chicken intestinal epithelial cells and damage these cells. Also, the immune systems of chickens likely deal with the bacterium differently. Chickens are a great model for investigating how disease by C. jejuni is prevented." -Dr. David Hendrixson



Immobilizing colonization and mobility

Dr. David Hendrixson, associate professor of microbiology, is conducting research aimed at ridding the world of one of the most common and severe forms of diarrheal disease in humans. *Campylobacter jejuni (C. jejuni)* is a bacterial pathogen that colonizes the gastrointestinal tracts of humans and animals, particularly chickens and other types of poultry.

It often is spread among flocks in feces and infects humans through their consumption of contaminated poultry. C. jejuni has also sickened consumers of other meats and unpasteurized milk. The bacterium is harmless in livestock but it can cause mild to severe diarrhea when passed to humans.

"The chicken gastrointestinal tract has adapted to the presence of *C. jejuni,*" Dr. Hendrixson said. "Unlike in humans, C. jejuni does not invade chicken intestinal epithelial cells and damage these cells. Also, the immune systems of chickens likely deal with the

bacterium differently. Both of these factors contribute to the reasons why chickens don't become ill due to C. jejuni infections. Chickens are a great model for investigating how disease by C. jejuni is prevented."

Dr. Hendrixson's lab is studying the genes the bacterium needs to live within an avian host in hopes that this understanding may lead to strategies to eradicate it from chickens and thus decrease the amount of the bacterium in human food.

He and his UT Southwestern colleagues have identified many factors C. jejuni requires for the colonization of poultry and are analyzing how these factors benefit bacteria growth and might be targets for future vaccines.

Dr. Hendrixson also is focusing on the genes involved in the function and regulation of the flagellum C. jejuni produces, which allows the bug to propel itself throughout a host's gastrointestinal tract. Flagellum is a tail-like projection that protrudes from the pathogen and can move it toward various nutrients for growth. Bacteria create only a certain number of flagella and at very specific locations.

"Scientists are still unsure how C. jejuni, or similar bacteria, know to create an exact number of flagella and at specific locations," said Dr. Hendrixson. "We want to understand these spacial and numerical parameters, because if we know how C. jejuni builds its flagellum, we may be able to disrupt the process and immobilize the pathogen."

Protecting the kitchen

The global incidence of foodborne disease is difficult to estimate. As international shipping in the food industry continues to expand, so does the possibility of bacterial pathogens crossing borders.

There are steps consumers can take to try to keep a market trip from leading to a stay in the hospital. The CDC reports that raw meat and poultry, raw eggs, unpasteurized milk and raw shellfish are the foods most likely to be contaminated. Lona Sandon, assistant professor of clinical nutrition and a spokeswoman for the American Dietetic Association, stresses that all meat, poultry and eggs should be cooked thoroughly. She recommends using a thermometer to measure the internal temperature of meat to ensure it is cooked sufficiently to kill bacteria. Most meats should be cooked to 165 degrees and leftovers also need to be heated to this temperature.



"It's also important to avoid cross-contamination of one food with another," said Ms. Sandon. "Wash hands, utensils and cutting boards after they have been in contact with raw meat or poultry and before you touch another food. Place the cooked meat on a separate dish, rather than one that has held raw meat. And be sure to refrigerate leftovers promptly. Bacteria can grow quickly at room temperature." Regarding vegetables and fruits, Ms. Sandon says washing these foods with running water is the best way to remove unwanted pathogens. She warns that the cut surface on fruits and vegetables is a prime environment for bacteria growth. It also is important for consumers to be mindful of slicing the foods on clean

Yet despite such precautionary measures everyone, no matter their location in the world, is susceptible to illness caused by foodborne bugs. And the clock is ticking as more and more of these bacteria are becoming immune to the effects of antibiotics. Over time bacteria have adapted to make human cells work to their advantage. UT Southwestern researchers are determined to turn the tables on them.

cutting surfaces.

"Wash hands, utensils and cutting boards after they have been in contact with raw meat or poultry and before you touch another food. Place the cooked meat on a separate dish, rather than one that has held raw meat. And be sure to refrigerate leftovers promptly. Bacteria can grow quickly at room temperature."

-Lona Sandon

What it takes to become a world-class physician



Knowledge, skill and years and years of practice from basic anatomy classes as a first-year medical student to training as an intern to subspecialty expertise as a fellow and beyond

It's one of life's most vulnerable moments wondering exactly what's wrong as you wait for the doctor to enter the room. Was it a heart attack? A stroke? Is it cancer, or a brain tumor? Your mind reels ... How bad is it? Is there a treatment? Is surgery needed?

Eventually, we all look into the face of our physician – searching for answers to some of the most personal, complex and often frightening problems we will ever face.

Each year, UT Southwestern Medical Center's teams of physicians look into the eyes of about 100,000 hospitalized patients – and even more individuals during nearly 2 million visits at outpatient clinics - to provide answers to how their illnesses might be diagnosed, treated or surgically addressed.

When they arrive at UT Southwestern, these patients tap into a unique brain trust. It includes five Nobel laureates, 12 Howard Hughes Medical Institute investigators, 19 members of the National Academy of Sciences, 20 members of the Institute of Medicine and 15 members of the American Academy of Arts and Sciences. It's a brain trust forged of boardcertified surgeons, specialists, sub-specialists and internists, past and present presidents of national medical societies, investigators for National Institutes of Health studies, and chairs of national committees in fields from pediatrics to plastic surgery, from breast care to neurology. It's a trust clinically recognized nationally in six specialties by U.S. News & World Report and delivered in the top-ranked hospital in the Dallas-Fort Worth region.



Many members of UT Southwestern's faculty have written the textbooks used to teach others or have served as editors on prestigious peer-reviewed journals such as the Journal of the American Medical Association and the New England Journal of Medicine, publications the medical profession relies on to stay current regarding cutting-edge treatments and procedures.

Yet underlying that cavalcade of expertise and excellence are the humble beginnings – the first steps every doctor takes to become a physician.

Founded in 1943, UT Southwestern Medical School has graduated nearly 10,000 physicians. This academic year, the medical school will train nearly 1,000 medical students and almost 1,500 clinical residents. UT Southwestern offers more than 30 residency programs and more than 60 clinical subspecialties fellowships in the Dallas area. More than 60 percent of physicians in the Dallas area earned their degrees from UT Southwestern, and more remain affiliated with the university.

Preparing those doctors is more than just part of UT Southwestern's mission for academic medicine practitioners; it is a duty, a sacred one taken as seriously as the physician's oath. While we, as patients and consumers, may catch a glimpse of the medical world when we are ill or injured, our doctors – even the youngest among them – have been immersed in medicine for at least the better part of a decade, most far longer. And the amount of knowledge they acquire, and the multitude more at their disposal, is simply astounding.

THE UNIVERSITY OF TEXAS SOUTHWESTERN MEDICAL CENTER

U.S. News & World Report ranks UT Southwestern in the Top 25 in the nation for both research and primary care in its listing of Best Medical Schools for 2012. These accolades, as well as a decades-long reputation for superior education and training, drive a select student body. Virtually all of these students are among the smartest in their undergraduate class.



SO JUST HOW MUCH DOES YOUR DOCTOR KNOW?

Consider: • They've learned an encompassing lexicon – from diseases

to medicines to procedures – an exacting vocabulary all its own. They have mastered myriad instruments, how to use them and how not to use them.

- They have dedicated years of observing, learning and appreciating cellular reactions; where and how muscles connect; how glands deliver various enzymes and why; how organs work in concert and the signs that they aren't functioning properly; which test can pinpoint troubles and which can rule them out.
- They are able to tell patients what that rash is; whether their limb is really broken; and when they need to do something about our ever-declining capabilities to see and hear.
- They've learned to give injections, to determine which drugs fight infections and to perform surgery.
- They have learned to handle the human factor, such as how to share with someone that they are facing cancer, need bypass surgery or have a complicated pregnancy. They have learned not to panic when the diagnosis is not easy, how to search medical literature for a similar case or situation, and how to determine their patients' best treatment options.
- From years of classroom and clinical training, they have learned statistical analysis so they can filter cause-and-effect from mere association. They have learned the proper handling

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of hazardous, toxic and medical wastes, and have memorized billing codes and mastered electronic medical records to ensure complete and correct paperwork and charts.

They have learned all this for dozens of types of cancers, hundreds of cardiology problems and thousands of other diseases and conditions.

BECOMING AN M.D.



Becoming a doctor is not really a moment; it is at best an evolutionary process. "What a student really has to

do is learn how to be a student for life," noted Dr. J. Gregory Fitz, executive vice president for academic affairs, provost and dean of UT Southwestern Medical School.

Becoming a doctor involves a gauntlet of years spent, knowledge learned and experience gained. Those who make the decision to shoulder such challenges, responsibilities, oaths and heartaches do so because their hearts and heads told them to do so.

MEDICAL SCHOOL



UT Southwestern Medical School – the 68th established in the country and the second of four established in the Univer-

sity of Texas system - offers six medical degrees, from Doctor of Medicine to combinations that include master and Ph.D. degrees.

U.S. News & World Report ranks UT Southwestern in the Top 25 in the nation for both

research and primary care in its listing of Best Medical Schools for 2012. And for three of the past four years, UT Southwestern has been ranked as the nation's top medical school for Hispanics by *Hispanic Business* magazine, which takes into account academic excellence, enrollment, faculty, student services and retention rates.

These accolades, as well as a decades-long reputation for superior education and training, drive a select student body. Only about 230 of the roughly 3,500 students applying annually to UT Southwestern Medical School are accepted. That's a 6.5 percent acceptance rate.

"Virtually all of these students were among the smartest in their undergraduate class. Many were valedictorians. They are all very bright," said Wes Norred, vice president for student and alumni affairs. "But then you arrive at medical school, you're not the smartest kid in the class anymore. It's filled with the smartest kids in the class. That's an adjustment for some.

"Another immediate adjustment is that the volume of material to be learned is huge. A lot of people say it's like drinking from a fire hose."

YEAR ONE



The first-year curriculum at UT Southwestern is nine months long. It begins with a study of the typical human body and its

processes at the molecular and cellular levels. Biochemistry, genetics, anatomy and embryology are presented concurrently for the first portion of the year, melding the concepts of macromolecular and cellular interactions within tissues. Students take introductory courses in clinical ethics in medicine and critical thinking; by spring they are taking interdisciplinary courses in physiology and neuroscience, as well as courses in cell biology and human behavior and psychopathology. An 11-week summer break at the end of the first year often is filled with clinical training or basic science and clinical research opportunities, providing simultaneous exposures to the practice world.

During the first year, students learn how to take a patient's history and to perform a detailed physical exam on "standardized patients," receiving careful instruction from their mentors and detailed feedback on their clinical skills. "Standardized patients" are people trained and scripted for various diseases to provide a consistent, reproducible presentation of a clinical case. This exercise is digitally recorded for later review by the student and mentors, and the trained "patients" also provide their own feedback.



YEAR TWO

In the second year, the instructional perspective shifts to organ systems: clinical medicine, microbiology, pathology and

pharmacology laid out in 12 specialized blocks spread over another nine-month period. Certification in advanced cardiac life support, a requirement for graduation, is usually completed after the second year, and students typically take Step 1 of the three-part United States Medical Licensure Exam (USMLE). All portions must be completed before being permitted to practice medicine domestically. Step 1 is an eight-hour, computer-based exam consisting of 322 multiple-choice questions.

Simultaneous exposure to the clinical world also awaits students the second year. Among those opportunities is The Monday Clinic, a free weekly clinic for adult patients operated under the supervision of UT Southwestern physicians by volunteer medical students who receive special training before participating. "Hypothetical scenarios in class are one thing, but being able to use the knowledge I gained in my first-year medical education at The Monday Clinic was a refreshing reminder of how important our studies truly are," said Sandeep Mehta, a second-year medical student.



A typical day on hospital wards consists of morning rounds, a noon conference and afternoon rounds, in addition to a daily fare of reading journal articles and attending conferences, grand rounds and case presentations.



YEAR THREE

In the third year, the curriculum lengthens to 11 months, and the focus shifts to the first of two years of intense clinical

training and experiences involving direct patient care. Though some medical schools have moved to more of an observer-type role for their students with no on-call time, medical students at UT Southwestern are integral to patient-care teams. They take overnight calls and have real responsibilities and exposure to the care process.

"This is a school that values learning by doing," said Dr. Fitz, professor of internal medicine who holds the Nadine and Tom Craddick Distinguished Chair in Medical Science and the Atticus James Gill, M.D., Chair in Medical Science.

A typical day on hospital wards consists of morning rounds, a noon conference and afternoon rounds, in addition to a daily fare of reading journal articles and attending conferences, grand rounds and case presentations. Departmental rotations include family medicine, internal medicine, neurology and neurotherapeutics, obstetrics and gynecology, pediatrics, psychiatry, and surgery in hospital and outpatient clinics as well as public and private practices. A typical schedule includes: 12 weeks of internal medicine, eight weeks of pediatric and surgery rounds, six weeks of psychiatry and OB/ GYN, and four weeks of family medicine and neurology and neurotherapeutics.

Third-year students take initial patient histories, perform initial physical exams, write daily progress notes on their assigned patients and present them on daily rounds. During the OB/GYN rotation and under supervision, students assist in delivering babies in uncomplicated pregnancies, assist in managing complicated pregnancies during the labor and delivery process, and follow patients postpartum. In the surgical rotation, emphasis is on the underlying pathophysiology rather than technical aspects, but students are fully involved in the daily care of surgical patients and participate in diagnostic and therapeutic decision-making.

"Students often tell me that they are amazed by the fact that even on their first day of their clinical rotations, when they often feel insecure and unprepared, patients commonly

welcome their participation in their care and put a lot of faith and confidence in them," said Dr. Angela Mihalic, associate dean for student affairs and associate professor of pediatrics. "Students are truly humbled by the sacred trust placed in them as patients reveal their most intimate thoughts, fears and concerns associated with their health. This faith and confidence provides students with a mission and a directive to do everything in their power to develop their knowledge and clinical skills to be able to live up to the expectations placed in them and be worthy of this trust."

In addition, a number of simulated environments provide an opportunity for students to learn, practice and hone those clinical skills. The SimCenter offers a small group teaching center where students can learn and practice skills on high-fidelity simulators that are close replicas of human patients. Students in surgical rotations can practice skills in the Center for Minimally Invasive Surgery, a hands-on locale

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PHYSICIAN ASSISTANT PROGRAM CELEBRATES 40 YEARS

While well known and respected for its medical school, UT Southwestern Medical Center also is known in health care circles for its top physician assistant training program.

In 2012. UT Southwestern School of Health Professions celebrates 40 years graduating physician assistants as one of the first, and now among the top, programs in the nation. UT Southwestern's Master of Physician Assistant Studies Program, ranked eighth in the nation by U.S. News & World Report in "America's Best Graduate Schools 2012," admits only a small fraction of those who apply for the 31-month degree program. For the class commencing in 2011, the school accepted just 36 of nearly 1,100 applicants.

"It's enormously gratifying to see these kinds of accolades for our program as ours and other programs have matured over the decades," said Dr. P. Eugene Jones, chair and program director for the Department of Physician Assistant Studies. "But the real benefit is to the thousands of patients who increasingly depend on highly qualified physician assistants to help provide care."

Physician assistants practice under doctor supervision. They take medical histories, conduct physical exams, diagnose and treat illnesses, order and interpret tests, provide counseling on preventive health care, develop treatment plans, assist in surgery and prescribe medications. More than 81,000 certified PAs practice in primary care and most medical specialties, according to the American Academy of Physician Assistants.

PAs are one of the nation's fastestgrowing segments of health care, according to the academy. The U.S. Bureau of Labor Statistics projected that the number of PA jobs would increase by 27 percent between 2006 and 2016.

Wanting to deliver hands-on health care often is the driving factor for students. That was the case for Dr. Tina Kaufman about 15 years ago when she began UT Southwestern's physician assistant program, allowing her to combine interests in research, teaching and indigent care.

"When I went into PA school, I knew I wanted to do primary care and I knew I wanted to do indigent care. That was really my focus," said Dr. Kaufman, who became the first physician assistant in the Internal Medicine Clinic at Parkland Memorial Hospital, where she had trained. She went on to establish training clinics for residents to learn about exercise prescription and counseling, chronic pain, smoking cessation and injections.

Dr. Kaufman, who majored in exercise science in college, already had earned a Ph.D. in physiology and completed two postdoctoral fellowships at UT Southwestern – in pediatric cardiology and in surgery - before joining the PA program in 1996. She recently joined the faculty at Oregon Health and Science University as assistant professor in preventive cardiology and cardiac rehabilitation in the Division of Cardiovascular Medicine.

When recounting her UT Southwestern experience, Dr. Kaufman said, "I can't think of anywhere else I could have gotten the training and fulfillment that I've gotten from my patients." After graduation and certification,

today's physician assistants have a host of areas to consider for additional study and specialization. These include cardiothoracic surgery, dermatology, emergency medicine, neonatology, neurology, neurological surgery, obstetrics/gynecology, oncology, orthopaedic surgery, pediatrics, psychiatry, rheumatology, surgery and urology.

The concept of physician assistants was first introduced in the 1960s, with the first class graduating in 1967 from a program established at Duke University Medical Center. The program included



"It's enormously gratifying to see these kinds of accolades for our program as ours and other programs have matured over the decades." - Dr. P. Eugene Jones

mostly Navy corpsmen with medical skills developed during their service, and it was viewed as an opportunity to help tackle a shortage of primary care doctors at the time. The initial training was based on the expedited training developed for military doctors during World War II. By 1968, the American Association of Physician Assistants was created, and in 1971 Congress apportioned \$4 million to launch physician assistant programs through the **Comprehensive Health Manpower Training** Act. That same year, a number of professional organizations, including the American Medical Association, the American College of Physicians and the American Academy of Pediatrics, agreed to minimum standards. UT Southwestern launched its physician assistant degree program through the graduate school in 1972.

The curriculum for physician assistants emphasizes both academic learning and hands-on clinical training. Students begin with four semesters of lecture and bedside demonstration in medical and behavioral sciences as the foundation. Four additional semesters of clinical rotations in a wide range of disciplines and settings follow, mainly at Parkland Memorial Hospital, but also through rotations in other affiliated hospitals, clinics, private physician practices, and long-term care facilities. At the end of 30 months, successful students receive a Master of Physician Assistant Studies degree and are eligible for the Physician Assistant National Certifying Examination required to practice. In the past five years, 99 percent of UT Southwestern graduates have passed the exam on the first try.



designed for learning and practicing surgical skills, such as knot tying, suturing and videoendoscopic techniques.

Third-year students also generally take the two-part Step 2 USMLE. The two parts cover clinical knowledge and clinical skills. Passing each is a requirement for graduation.



YEAR FOUR

Fourth-year students complete rotations that prepare them for internships and to apply for residency positions. During pariod, students select four

this 10-month period, students select four, four-week electives from Acute Care Clerkship, Ambulatory Care Clerkship, Sub-internship – all completed at UT Southwestern – and other electives that can be completed at UT Southwestern or elsewhere.

The Acute Care Clerkship offers instruction in the diagnosis and management of an acutely ill or injured patient, with rotations from a variety of clinical settings, including intensive care units, critical care services and emergency departments. The selection sites for this clerkship include Parkland Memorial Hospital's burn ICU, critical care unit, emergency department, neonatal ICU, surgical ICU and trauma service; Dallas Veterans Affairs Medical Center's cardiovascular anesthesia and surgical ICU; and Children's Medical Center Dallas' emergency department, pediatric ICU and pediatric cardiac critical care unit.

"The hospitals are wonderful places to train because of their size and the volume of

patients. The entire staff is all about getting students involved in patient care and having them be part of the team," said Dr. Rachel Jamison, Class of 2010.

In the Ambulatory Care Clerkship, students spend one month in outpatient clinics or private physicians' offices for internal medicine, family medicine, women's health, urology or ophthalmology.

In the Medicine Sub-Internship, students spend four weeks on an inpatient service in internal medicine, pediatrics, obstetrics and gynecology, or surgery.

By this point, students are an integrated part of the care team. They interview patients, obtain vital information for patient care, interpret data, discuss the treatment plan with the patient and family, promote general health maintenance and disease prevention, and consult with specialty services and teams to coordinate care. While closely supervised, fourth-year students are able to provide a diagnosis and offer treatment plans, and demonstrate they can effectively communicate with the health care teams, patients and patients' families.

Four months of the fourth year of medical school are available for electives selected from more than 100 courses offered by departments and divisions. The electives are designed to provide specific, extended experience in areas of particular interest to the student.

"I've seen them ecstatic with their acceptance into medical school. I've seen them consumed by the overwhelming volume of knowledge they must master. I've seen them evolve into physicians," said Dr. James Wagner, associate dean for student affairs and associate professor of internal medicine, who has witnessed more than 15 years of graduating classes.

INTERNS AND RESIDENTS



With their medical degree in hand, quite an accomplishment, they still stand at the bottom rung of the next ladder to be

climbed. Interns are M.D.s in their first year after graduating medical school. The internship can be part of a multi-year residency, making the intern the equivalent of a first-year resident; or the internship may be a stand-alone program preceding a residency. A residency lasts at least three years and can extend up to six or seven years for surgical specialties.

A requirement for practicing independently is passing Step 3 of the USMLE. Step 3 is the final exam of the three-part licensing exam and is often taken after the first year of residency or internship. Step 3 is a two-day exam that covers several hundred multiple-choice items. Residency involves clinical training targeted to a specific specialty such as internal medicine, pediatrics or surgery, as opposed to the more generalized teachings in medical school. While students experience a meteoric rise in knowledge and skills during medical school, it is during residency where those skills are hammered, hardened and honed so that each doctor is prepared to practice medicine independently.

Training for emergency medicine residents at UT Southwestern serves as an ideal example. Emergency medicine residency training includes the emergency departments of Parkland Memorial Hospital and Children's Medical Center Dallas, both recognized elite Level I Trauma Centers and among the busiest in the nation in their respective categories. As an integrated system, the departments triage more than 200,000 adults and children annually.

Emergency medicine residents perform resuscitations on every shift. EM residents participate in rotations in pediatric EM, adult EM, toxicology and disaster medicine, as well as receive training in ground and air transport. They have opportunities to practice event medicine – caring for emergencies at large events such as football and baseball games – and practice in other countries. Emergency medicine residents also participate in disaster response

By the time UT Southwestern students and trainees exit, years of education and training have provided a rock-solid foundation to handle those most vulnerable moments of life they will experience with their patients.



efforts locally. During Hurricane Katrina in 2005, for example, UT Southwestern residents helped treat the more than 8,000 patients seen in the supervised EM unit at the Dallas Convention Center, operated by UT Southwestern physicians.

An often perpetuated misconception is that residents should have an over-the-shoulder view in the care of a patient in a passive, watch-and-learn capacity. In reality, residency is the time in which the new M.D. steps forward and the attending supervising physician must begin to gradually step back.

It is hardly an all-or-nothing proposition. Each step – forward for the resident and backing away for the attending – is a graduated, carefully synchronized transition. Called proficiency-based training, the process allows the resident to step forward only after successfully demonstrating prior proficiency of the skill needed to the attending, who takes a step back to supervise and observe.

"If you look at that scenario, it is similar to how they do things in such sports as gymnastics," said Dr. Robert Rege, chairman of surgery and a noted pioneer in educating surgical residents. "You are on a low beam first, and when you can perform certain tasks, then you are allowed to go to a higher beam. That would be What has changed in the past century is the amount of information the physician must process and retain. It is estimated that by 2020, medical knowledge will double approximately every four months.

proficiency-based training. You have to show competency at certain skills before you can go into training for the next level of skills."

It is critical to allow residents to perform examinations, order tests, diagnose illnesses, craft treatment plans and perform surgical procedures with graduated independence – with more experienced physicians still on hand. This assures that when residency training is completed, the resident doctors are well-prepared to handle the patients they will see independently.

"If someone wants to say it's immoral, because they're letting doctors practice on patients, my answer to that is no, it is immoral to let somebody into the community who is not qualified to take care of you," said Dr. Rege, who holds the Hall and Mary Lucile Shannon Distinguished Chair in Surgery. "Within some boundary that keeps it as safe as possible, we do need to allow that responsibility to be taken.

"This is a school that values learning by doing." — Dr. Gregory Fitz



"It is how every major teaching hospital in the country works. You're never going to be able to do something independently if you never have a chance first."

It is also why institutions like UT Southwestern, where students are immersed in some aspect of clinical care from year one, find special favor among those training to become doctors and those recruiting for their residency programs.

"The quality of the scientific curriculum at UT Southwestern is unquestionable, and the clinical training, one finds out upon starting residency, is second to none. You learn how to be a self-sufficient physician years before you ever start internship," said Dr. Scott Paulson, Class of 2008.

FELLOWSHIPS AND BEYOND

While the conclusion of residency programs allows physicians who have passed the

requisite licensing tests to practice independently, many choose to continue to an even higher plane – becoming a fellow. Fellowships are offered for expertise in subspecialties like cardiology, gastroenterology and orthopaedics, and typically involve a balance of research and clinical care in the specified subspecialty.

In emergency medicine, for example, fellowship opportunities include toxicology, government emergency medical services and security, practice management and health care policy, and pediatric emergency medicine. UT Southwestern's Department of Pediatrics has more than 90 postdoctoral trainees in the sub-specialty training programs overseen by its divisions.

To retain a medical license, physicians also must attend and complete continuing medical education courses and accumulate credits annually. Last year, UT Southwestern faculty members provided continuing medical education training to nearly 38,600 participants at almost 260 activities.



"To be a great physician, Dr. William Osler said in a famous speech to residents, you have to have a clear head and a kind heart. I'm not sure that's changed in the 100 years since that statement was made." – Dr. David Johnson (right)

THE FUTURE OF MEDICAL DOCTORS

More than 100 years ago, many medical schools offered nothing more than lectures. This inad-

equacy led to a foundational critique in 1908 called The Flexner Report, which laid out the fundamentals of what a medical education should be required to provide – and it remains the standard today: a robust balance of biological and anatomical understanding, coupled with hands-on practice of medicine so doctors have the knowledge and experience needed when they leave medical school.

Dr. William Osler, still considered the father of modern medicine, created the first residency program to train specialists, emphasizing the need for students to go beyond lecture halls to learn hands-on, bedside care.

"To be a great physician, he said in a famous speech to residents, you have to have a clear head and a kind heart. I'm not sure that's changed in the 100 years since that statement was made," said Dr. David Johnson, chairman of internal medicine at UT Southwestern.

What has changed in the past century is the amount of information the physician must process and retain. It is estimated that by 2020, medical knowledge will double approximately every four months.

While that may require changes in how doctors access information – spending more time at a computer, for instance – it shouldn't mean physicians simply become providers. As Dr. Fitz hc Ch op ed to ga ity th tra ha tra ha th

By the time UT Southwestern students and trainees exit, years of education and training have provided a rock-solid foundation to handle those most vulnerable moments of life they will experience with their patients. "By the end, idealism turns into seasoned wisdom," Dr. Wagner said. "They learn their own limits, the limits of our knowledge, and the power of a kind word, gentle touch and simply being there. They become accustomed to the miracle of birth, the inevitability of death, the exhilaration of cure and the devastation of failure. The magnetic pole for their moral compass changes from within themselves to within the well-being of their patients."

noted, they have to become lifelong students. "Texans actually believe there is nothing they can't do. They believe they can do everything. I like that attitude," said Dr. Johnson, holder of the Donald W. Seldin Distinguished Chair in Internal Medicine, adding that the opportunity to help define the future of medical education was among the reasons he decided to come to UT Southwestern. "It's not arrogance. It's sort of a roll-up-your-sleeves mentality. You get that precise feeling when you walk through the doors here." (special section)

"What makes us

unique is that we

take care of these

two big populations

- sleep disorders and

breathing disorders."

-Dr. Won Lee

Clinic treats sleep and breathing disorders By Jeff Carlton

If anyone knows the importance of a good night's sleep, it's Roland Dickey.

The owner of the Dallas-based chain of barbecue restaurants that bears his name, Mr. Dickey said he'd wake up exhausted, fight off sleep throughout the day and sometimes find himself nodding off while driving.

He sought treatment at UT Southwestern Medical Center's Clinical Center for Sleep and Breathing Disorders, where new medications and treatments are dawning in the world of sleep medicine. One night at the center brought an end to Mr. Dickey's sleepdeprived life.

"I felt the difference immediately," Mr. Dickey said. "I was jumping out of bed with a lot more energy and it lasted all day." Dr. Won Lee, medical director of the sleep center, located at University Hospital - St. Paul, understands that the right amount of shut-eye translates into a restful peace of mind and, more importantly, improved health.

Unlike many sleep centers, UT Southwestern focuses not only on caring for patients with primary sleep disorders but also those with secondary breathing disorders resulting from progressive neuromuscular diseases.

"What makes us unique is that we take care of these two big populations - sleep disorders and breathing disorders," said Dr. Lee, assistant professor of internal medicine.

Patients with chronic sleep loss are at increased risk for hypertension, diabetes, obesity, depression, heart attack and stroke, according to the Institute of Medicine, which has identified sleeping disorders as an unmet public health problem.

In addition, researchers have linked sleep loss and sleeping disorders to more than \$63 billion in lost productivity in the U.S. annually and to 20 percent of all serious automobile crashes.

At its 6,000-square-foot facility on the second floor of Professional Office Building 2 on UT Southwestern's West Campus, the Center for Sleep and Breathing Disorders addresses these issues head on. The center is among the nation's most advanced and is accredited by the American Academy of Sleep Medicine, "which guarantees that the quality of our sleep lab testing is exceptional," Dr. Lee said.

The busy clinical center, which conducts about 120 sleep studies a month, has a six-bed sleep laboratory with private bathrooms in

each patient room, and spaces for physician and staff member offices, patient counseling areas and more. Patient treatment starts with a comprehensive questionnaire that leads to an individualized plan based on each person's specific needs and therapy goals.

Treating such a broad base of patients requires a multidisciplinary approach that an academic medical center such as UT Southwestern is best equipped to provide. The center's team of pulmonologists and neurologists are all certified or board eligible in sleep medicine. The collaborative effort between pulmonology and neurology is further bolstered by a strong relationship with UT Southwestern physicians who specialize in otolaryngology and oral maxillofacial surgery, as well as a nurse practitioner and a full staff of sleep technologists who are dually trained in both sleep medicine and respiratory therapy.

This team approach ensures that the center can meet the respiratory and neurological needs of all its patients.

Those needs can be vast and varied. The center sees patients suffering from some of the more common sleep problems, including sleep apnea, insomnia, restless leg syndrome, narcolepsy and circadian rhythm disorders. The breathing disorders program, led by Dr. Joseph Viroslav, professor of internal medicine, focuses on the assessment and management of respiratory problems in patients with neuromuscular diseases, including amyotrophic lateral sclerosis, muscular dystrophy, spinal cord injuries and scoliosis.

The center features state-of-the-art diagnostic and treatment equipment, including



advanced monitoring software that collects data on sleep parameters; sophisticated polysomnogram usage and subsequent interpretations; and use and education of patients on continuous and bilevel positive airway pressure devices (better known as CPAP and **BPAP** machines).

Open since 2007, the center already has established itself as the region's premier facility for sleeping and breathing disorders.

"There is not always a lot we can do in medicine that can make an immediate impact on someone's quality of life," Dr. Lee said. "But when we effectively treat sleeping disorders, people immediately feel better. And the opportunity to see that day in and day out is very satisfying."

For more information about sleep therapy, please call 214-645-5337.

Targeted therapy for advanced gynecologic cancers

By Robin Russell

Advanced endometrial cancer patients are typically treated with both surgery and chemotherapy, but long-term prognosis remains poor. The five-year survival rate for Stage 3 patients is just 50 percent; for Stage 4, it drops to 20 percent. Optimizing additional therapy for advanced endometrial cancers remains an area of significant research interest.

Now, UT Southwestern researchers are working with the Gynecologic Oncology Group (GOG), a nonprofit organization dedicated to research in gynecologic cancer, and supported by the National Cancer Institute of the National Institutes of Health. They are seeking to improve outcomes by offering a national clinical trial in hopes that one or more of three biologic targeted agents, in combination with chemotherapy, will be more effective than the standard care for endometrial cancer, or cancer of the uterine lining.

For advanced endometrial cancer, chemotherapy typically consists of carboplatin and paclitaxel, given every three weeks for a total of six treatments. In the current trial, GOG 86 P, patients are randomly assigned to also receive one of three therapeutic agents shown to be effective in other types of cancer.

"This is useful for patients with advanced or recurrent endometrial cancer because it offers them the opportunity to receive a targeted agent that would not be available otherwise.

These types of trials will hopefully provide greater benefit for endometrial cancer patients," said Dr. Jayanthi Lea, an assistant professor in the division of gynecologic oncology. "The design of this trial is enticing exploring three novel agents, using a randomized three-armed study pattern."

Endometrial cancers are the most common gynecologic cancers in the U.S., with over 35,000 women diagnosed each year, and the third-most common cause of gynecologic cancer death, behind ovarian and cervical cancer.

Symptoms include postmenopausal vaginal bleeding, irregular vaginal bleeding in premenopausal women, pelvic pain and pelvic mass. The cornerstone of treatment is surgical removal of the uterus, tubes, ovaries and lymph nodes to remove the bulk of the disease and to assess the status of the lymph nodes, the size and histology of the tumor, the depth of invasion, and the stage of the disease. Advanced stage patients also receive chemotherapy.

Patients in the GOG 86 P trial randomly receive either an mTOR inhibitor, which inhibits some of the enzymes needed for cell growth; bevacizumab, which is an angiogenetic activator and can block enzymes needed for cell growth; or a novel antimitotic agent, which inhibits cancer growth by stopping cell division in combination with bevacizumab. Each is given in combination with the one or two standard chemotherapy drugs. Maintenance treatment will be given following a planned course of chemotherapy.

Researchers participating in the GOG 86 P clinical trial hope to test 330 patients in a 23-month period at multiple medical centers across the U.S. Several gynecologic oncologists in the Dallas-Fort Worth area already have referred patients to UT Southwestern for this trial, Dr. Lea said.

About 45 GOG clinical trials are active at any one time for patients with a variety of gynecologic malignancies. UT Southwestern currently has 19 GOG trials open. For more information about GOG clinical trials, please call 214-645-4673.



"The design of this trial is enticing - exploring three novel agents, using a randomized three-armed study pattern."

—Dr. Jayanthi Lea

(special section)

"There are probably

and several genes

have already been

—Dr. Deborah Friedman

discovered."

many genes involved

Making headway on headaches

By Russell Rian

Only about half those suspected of having it are ever diagnosed.

- There's no cure.
- No known cause yet.

Its triggers can seem little more than a jumble of endless possibilities.

And effective treatments are sometimes elusive.

Migraine pain has proven an exasperating headache not only for sufferers, but for the physicians and researchers engaged in tracing those triggers, targeting effective treatments and tracking down its genetic causes.

More than 35 million Americans report suffering from the pain of migraines, which has become one of the most common reasons for missed work, second only to back pain. Migraines are about three times more common in women than men and are thought to be linked to estrogen fluctuations.

Half of all migraine sufferers have their first attack before the age of 12. Roughly 7 percent of children experience migraine pain, and children are more likely to have migraines if their parents also suffer them. Children suffering from migraines are absent from school twice as often as children who don't have them.

"Migraine is not just a headache," explains Dr. Deborah Friedman, professor of neurology and neurotherapeutics at UT Southwestern Medical Center and a national expert on headaches. "Many structures throughout the brain are involved in migraine to explain the pain, nausea, light and sound sensitivity, emotional changes, confusion and other symptoms of migraine. While there is still much to be learned, migraine research has flourished during the past 10 years."

People with recurrent migraines likely have a genetic predisposition to them, said Dr. Friedman, also a professor of ophthalmology. About 80 percent of sufferers report a family history of migraines, and a child has a 50 percent chance of having migraines if one parent suffers them and a 75 percent chance if both parents experience migraines, according to recent studies. People with other types of neurological disease such as epilepsy, as well as those with asthma and some psychiatric diseases such as depression or anxiety, also are more likely to experience migraines.

"There are probably many genes involved and several genes have already been discovered," Dr. Friedman said.

Research has shown that patients with frequent or severe migraines are best managed at a headache center like the Headache and Facial Pain Program being established at UT Southwestern under Dr. Friedman's direction.

The migraine brain is more "sensitive" to various trigger factors and to a process called cortical spreading depression (CSD), which is a wave of increased excitability of nerve cells, followed by decreased excitability and changes in blood flow. Researchers also have identified changes in and around the blood vessels that supply the lining of the brain and release of various chemicals in the brain that create pain and inflammation.

About 15 percent to 20 percent of people with migraines get an "aura," neurological symptoms that signal the onset of a migraine. An aura can last anywhere from five minutes to nearly an hour before fading as the migraine takes over. These can include visual cues wavy or jagged lines, flashing light or dots, blind spots and tunnel vision. Sufferers also may experience strange smells and sounds, tingling or numbness.



A proactive first step if you suspect migraines is to seek out migraine experts who can start ruling out other causes, such as tension or other types of headaches. Common indicators include a lack of relief from overthe-counter medications and severe headaches that occur on a routine or cyclical basis.

The program at UT Southwestern can offer the expertise of neurologists specializing in headache medicine, anesthesiologists who are pain management specialists, plastic surgeons with nerve decompression expertise, oromaxillofacial surgeons, physical therapists, psychologists, acupuncturists, nutritionists and specially trained support staff attuned to the sensitivities experienced by headache suffers. The program will include state-of-the-art outpatient and inpatient therapy.

In addition, UT Southwestern's plastic surgery faculty has surgical treatments for migraines if more traditional therapies don't provide relief. Dr. Jeffrey Janis, associate professor of plastic surgery, helped champion a technique that uses Botox – typically known for cosmetic uses - to help potential peripheral nerve trigger points that may be contributing to migraine pain. He also was involved in the development of surgical techniques based on anatomical studies to decompress these nerves in order to provide more long-lasting symptomatic relief.

In a recently published study, Dr. Janis corroborated the effectiveness of using Botox and surgery to treat migraine headaches, with participants reporting an average improvement of 85.5 percent over their original symptoms.

"This represents the type of clinical research into the effectiveness of new treatments we need," said Dr. Janis, chief of plastic surgery at Parkland Memorial Hospital. The new headache program has similar

research plans.

"We will conduct clinical research in headache disorders so our patients will have the opportunity to help determine the effectiveness of new treatments as they are in the development stage," Dr. Friedman noted.

Current research is targeting specific aspects of the migraine process, such as chemicals involved in the generation of inflammation, changes in blood vessels, and mediators of the pain process (CGRP, substance P, nitric oxide, serotonin receptors and others). In addition, Dr. Janis plans further research into possible compression points of peripheral nerves, proteomics of nerves and quality of life studies.

Nerves supplying muscles in the neck are connected to the circuits in the brain stem that are involved in migraines, so physical therapy and treatments directed at the neck are sometimes beneficial. Medical procedures, such as occipital nerve stimulation and transcranial magnetic stimulation, also may help patients who have severe migraines that cannot be controlled with conventional medications. Unfortunately, the solutions can have side effects, such as gastrointestinal disruption or increased likelihood of kidney stones. Dr. Friedman said staying hydrated can sometimes help avoid kidney stones, which still remain relatively rare. Previous research at UT Southwestern showed that long-term use of the popular migraine drug topiramate may make patients more likely to develop stones. People who took the drug for more than a year had chemical changes in their blood and urine that are associated with increased risk for kidney stone formation, according to research by Dr. Khashayar Sakhaee, chief of mineral metabolism and holder of the Laura Kim Pak Professorship in Mineral Metabolism Research and the BeautiControl Cosmetics Inc. Professorship in Mineral Metabolism and Osteoporosis.

From specialists in neurology to plastic

Drug prevention therapy generally involves anti-seizure medications, antidepressants or medications used for high blood pressure, such as calcium channel blockers and beta blockers. Drug therapy for pain relief may come in the form of pills, injections or even a nasal spray. Many migraine sufferers find relief from triptans, which help control pain and other symptoms such as nausea and sensitivity to light and noise.

surgeons, from physical therapists to nutritionists, from inpatient stays to outpatient therapy, UT Southwestern's Headache and Facial Pain Program will apply a multidisciplinary approach in matching each migraine patient with the most effective treatment options.

"We will conduct clinical research in headache disorders so our patients will have the opportunity to help determine the effectiveness of new treatments as they are in the development stage." -Dr. Deborah Friedman



The future of medicine, today.

UT SOUTHWESTERN Medical Center

FINANCIAL STATEMENT



normal.



FALL 2010

MEDICAL CENTER ESTABLISHES GLOBAL HEALTH OFFICE

UT Southwestern established an Office for Global Health to direct and develop training and research initiatives with partners around the world. Headed by Dr. Fiemu Nwariaku. the new office expands the institutional mission by integrating existing international activities, establishing new programs and training courses, and serving as a resource for faculty and students who wish to work abroad.

A task force for global health and care for the underserved was established in 2009 as part of the medical center's

DR. FIEMU NWARIAKU

strategic priorities. By fall 2011, UT Southwestern's farsighted initiative in support of its missions of education, research and patient care had resulted in three new institutional partnerships. The medical center's academic and scientific alliances are with Sun Yat-sen University and its First Affiliated Hospital in Guangzhou, China; with Rabin Medical Center in Israel: and with the University of Cape Town in South Africa.

UT Southwestern also has an agreement with the University of Paris for an international medical student exchange program.

SCIENTISTS CREATE EXPERIMENTAL ALZHEIMER'S VACCINE

After seven years of laboratory work, researchers at UT Southwestern have created an experimental vaccine against beta-amyloid, the small protein that forms plaques in the brain and is believed to contribute to the development of Alzheimer's disease.

The new experimental vaccine stimulated more than 10 times as many antibodies that bind to and eliminate betaamyloid compared with similar so-called DNA vaccines that the scientists tested in an animal study, said Dr. Roger Rosenberg, director of the Alzheimer's Disease Center at UT Southwestern.

A traditional vaccine – an injection of beta-amyloid protein itself into the arm – has been shown in other research to trigger an immune response, including the production of antibodies and other bodily defenses against beta-amyloid. However, the immune response to this type of vaccine sometimes caused significant brain swelling, so Dr. Rosenberg and his colleagues focused on developing a nontraditional DNA vaccine.

The new DNA vaccine does not contain beta-amyloid itself but instead a piece of the betaamyloid gene that codes for the protein. Once in the body, the DNA stimulated an immune response, including antibodies to beta-amyloid.

OBESITY-RELATED INFLAMMATION SPURS RESEARCH

Specialists at UT Southwestern are investigating how fat tissue "talks" to the brain and the liver to promote inflammationrelated disorders such as diabetes, heart disease and obesity. A five-year,

\$8 million grant from the

National Institutes of Health takes advantage of expertise across the UT Southwestern campus, including faculty in the Touchstone Center for Diabetes Research, the division of hypothalamic research, and the

complexity of how adipose [fat] talk to each other and how this

In 2007, the Task Force for phenomena related to inflammation, considered an underlying cause of metabolic

in the project will work individually on two common areas: identifying the critical sites for lipid-related inflammation in the periphery of the body as well as the brain, and identifying the biochemical signals that take place in the body after exposure to high-fat, lipid-rich foods.



departments of molecular genetics, internal medicine, and pharmacology. Dr. Philipp Scherer, director of the Touchstone Center, said the work will tackle the

tissue, the brain and the liver cross talk affects metabolism and inflammation.

Obesity Research at UT Southwestern (TORS) received a \$22 million NIH grant to enhance the institution's groundbreaking obesity research. Dr. Scherer said that while there is clearly synergy with the TORS grant, this new effort is unique because it is specifically focused on



WINTER 2010-2011

POTENTIAL NOVEL TREATMENT FOR TYPE 1 DIABETES IS UNCOVERED

Type 1 diabetes could be \mathbf{T} converted to a non-insulindependent disorder by eliminating the actions of a specific hormone, UT Southwestern research suggests.

The findings, in mice, show that insulin becomes completely superfluous and its absence does not cause diabetes or any other abnormality when the actions of glucagon are suppressed. Glucagon, a hormone produced by the pancreas, prevents low blood sugar levels in healthy individuals. It causes high blood sugar in people with type 1 diabetes.

Insulin treatment has been the gold standard for type 1 diabetes (insulin-dependent diabetes) in humans since its discovery in 1922. But even optimal regulation of type 1 diabetes with insulin alone cannot restore normal glucose tolerance. The new findings



DRS. ROGER UNGER AND YOUNG LEE

Sandra Childers became the 400th adult patient to receive a heart transplant at University Hospital - St. Paul. When Mrs. Childers hears her heartbeat, she still is

the test.

Through summer 2011,

amazed. She was without a pulse during the six-month span she wore a left ventricular assist device (LVAD) that helped her heart pump blood throughout her body. "Now I can actually hear and feel a heart. And it feels wonderful," she said. UT Southwestern heart transplant surgeons had performed 428 procedures at St. Paul alone, as well as additional transplants at the medical center's affiliated hospitals.

demonstrate that the elimination of glucagon action restores glucose tolerance to

In type 1 diabetes, which affects about 1 million people in the U.S., the pancreatic islet cells that produce insulin are destroyed. As a countermeasure to this destruction, type 1 diabetics currently must take insulin multiple times a day. In this study, UT Southwestern scientists led by Dr. Roger Unger, professor of internal medicine, tested how mice genetically altered to lack working glucagon receptors responded to an oral glucose tolerance test. The test measures the body's ability to metabolize, or clear, glucose from the bloodstream. The researchers found that the mice with normal insulin production but without functioning glucagon receptors responded normally to

BUSY TRANSPLANT TEAM RECORDS 400TH HEART PROCEDURE

LVADs allow patients to leave the hospital while they are waiting for a transplant.

Reaching the milestone was a testament to the commitment of many, including the surgical team of Dr. Mark Drazner, medical director of the Heart Failure and Cardiac Transplantation Program; Dr. Dan Meyer, professor of cardiovascular and thoracic surgery, whose group is instrumental in implanting the LVADs; and clinical nurse specialist Patricia Kaiser, who has been with the program since its beginning.

NANOTECHNOLOGY SUPPORT HELPS LAB MOVE FORWARD

Almost \$5 million in funding is moving the manufacturing and delivery of nanotechnologybased materials toward reality.

Nanotechnology has shown promise for both diagnosing and treating a range of medical conditions including cancer, autoimmune disease and human immunodeficiency virus, but developing a reliable way to manufacture those potentially lifesaving particles in large quantities for use in humans has remained a challenge.

Sen. Kay Bailey Hutchison was instrumental in securing resources from the Department of Defense to build a laboratory to research and produce carbonbased nanoparticles and to prepare biological materials that can then be delivered to patients. She also provided critical federal support for the construction of the Good Manufacturing Process (GMP) Nanoparticle and Cell Processing Lab on the UT Southwestern campus, in collaboration with UT Dallas.

Dr. James K.V. Willson, director of the Harold C. Simmons Cancer Center, the only National Cancer Institutedesignated center in North Texas, said that having this GMP facility will provide a unique opportunity for researchers to prepare cell materials – such as the hematopoietic stem cells routinely used to treat leukemia - for use in humans. The existing GMP laboratory in the Cancer Immunobiology Center is Food and Drug Administration-approved to produce antibodies and vaccines but not cells treated with these agents.

GMP facilities are regulated by the FDA and must be built to exacting federal specifications. These facilities remain under strict environmental control in order to assure the manufacture of sterile, potent and uncontaminated products for human therapies.

NEWBORN HEART MUSCLE HAS ABILITY TO REGENERATE

Researchers at UT Southwestern have discovered in mice that the mammalian newborn heart can heal itself completely. The scientists found that a portion of the heart removed during the first week after birth grew back wholly and correctly - as if nothing had happened.

Dr. Hesham Sadek, assistant professor of internal medicine, was co-senior author with Dr. Eric Olson, chairman of molecular biology and director of

the Nancy B. and Jake L. Hamon Center for Basic Research in Cancer. Dr. Sadek said the heart of newborn



DR. ERIC OLSON

mammals can fix itself; it just forgets how as it gets older. The challenge now is to find a way to remind the adult heart how to fix itself, an important step in the search for a cure for heart disease, the No. 1 killer in the developed world. The researchers found that

within three weeks of removing 15 percent of the newborn mouse heart, it was able to grow back the lost tissue completely, and as a result looked and functioned just like a normal heart. The researchers believe that uninjured beating heart cells, called cardiomyocytes, are a major source of the new cells.

Dr. Olson, who holds the Annie and Willie Nelson Professorship in Stem Cell Research and the Pogue Distinguished Chair in Research on Cardiac Birth Defects, said the inability of the adult heart to regenerate following injury represents a major barrier in cardiovascular medicine. "This work demonstrates that cardiac regeneration is possible in the mammalian heart during a window of time after birth. With this knowledge, we can next work to discover methods to reawaken cardiac regeneration in adulthood," he said.

SPRING 2011

CPRIT AWARDS \$36.7 MILLION FOR CANCER STUDIES

The Cancer Prevention and Research Institute of Texas (CPRIT) awarded more than \$36.7 million in new grants to UT Southwestern investigators to support cancer-related projects and recruit pre-eminent cancer investigators.

These awards, made after a rigorous peer-review process, resulted in UT Southwestern

receiving more funding than any other individual Texas institution in this round of grants. Awards to UT Southwestern

WILLSON

UT Southwestern leaders said support from CPRIT – now at \$115 million for more than 70 projects over the past two years – will accelerate dramatically the impact of UT Southwestern research on cancer care and illustrate the importance of teams of physicians and investigators working together to defeat the disease.

director of the Harold C. Simmons Cancer Center, said the awards fund projects highlighting the forefront of translating basic science and laboratory findings into practical treatments and technologies.

NEW HOSPITAL PROJECT SURGES WITH SUPPORT

The north end of campus began a four-year transformation, as the medical center swung into action for the new University Hospital, an \$800 million state-of-the-art facility slated to open in 2015. Several clinical service lines, offices and departments were relocated prior to site



researchers were part of \$116 million allocated for 22 projects at 16 Texas-based academic institutions and private firms by CPRIT, established in 2007 after Texas voters approved a constitutional amendment that authorized the state to fund cancer research and prevention programs.

Dr. James K.V. Willson,

CONSTRUCTION CREWS OPERATING HEAVY EQUIPMENT WORK ON THE FOUNDATION OF THE NEW UNIVERSITY HOSPITAL. UT SOUTHWESTERN LEADERS, COMMUNITY DIGNITARIES AND MEDICAL CENTER SUPPORTERS GATHERED AT THE SITE EARLIER IN CELEBRATION OF THE PROJECT'S START

preparation and building demolition, which began in the spring.

The 12-floor, 460-bed hospital – which will be the keystone facility on a 32-acre tract on the southwest side of Harry Hines Boulevard between Mockingbird Lane and Inwood Road – is an essential step in UT Southwestern's plan to become one of the nation's very top comprehensive academic medical centers.

The \$800 million hospital – designed by architectural firm RTKL Associates and being built by the Hunt Construction Group – will replace University Hospital - St. Paul, which cannot be expanded to handle growing capacity needs or economically renovated to incorporate the technology required to practice the medicine of the future. University Hospital - St. Paul will remain fully operational until the new 1.31-millionsquare-foot facility opens. The goal of UT Southwestern's Building the Future of Medicine capital campaign is to raise \$200 million in private support for the new University Hospital. When first announced, the campaign had already secured commitments of nearly \$62 million from community supporters. In addition, UT Southwestern physicians have committed \$200 million of their clinical earnings to support the project.

Dr. Daniel K. Podolsky, president of UT Southwestern, said the facility represents the forefront of design for patientcentric hospitals of the future, integrating best practices gathered from the nation's top medical facilities with the innovation and high standards of research and education that the medical center is known for around the world. [See story Page 34]



PEDIATRICIANS UNDERTAKE UNPRECEDENTED LONGITUDINAL CHILDREN'S STUDY

UT Southwestern pediatricians are helping lead the largest longterm study of children's health in the U.S.

The multicenter study will eventually follow 100,000 children nationwide from birth until age 21 to determine how various factors, including environmental and genetic ones, affect a child's health, development and quality of life. The findings may help form the basis of child health guidance, interventions and policy for future generations.

Dr. George Lister, former chairman of pediatrics, is principal investigator for the North Texas Children's Study Coalition, a collaboration of three UT System campuses and Battelle Memorial Research Institute in Columbus, Ohio. He said the significance of the study can't be overstated. The local core will be in Lamar County, about 100 miles northeast of UT Southwestern, along the Texas-Oklahoma border.

Now associate dean for education for UT Southwestern Medical School, Dr. Lister is collaborating on the study with Dr. Debra Cherry, principal investigator for the Lamar County location and occupational medicine physician at the UT Health Science Center at Tyler.

Dr. Lister said the team hopes to enroll and follow 1,000 Lamar County children. The undertaking is an observational research study rather than a clinical trial, so participants will not be asked to change their day-to-day routines or take any medicines or drugs. Staff

initially will collect data on pregnancies, such as the participant's diet, chemical exposure and emotional stress. Once new children are born, the researchers will begin collecting biological samples as well as environmental samples.

NATIONAL ACADEMY OF SCIENCES ELECTS PARADA TO MEMBERSHIP

The National Academy of Sciences elected Dr. Luis F. Parada, chairman of developmental biology, to membership, representing



DR. LUIS F. PARADA

one of the highest honors attainable by an American scientist.

With Dr. Parada's election, UT Southwestern now has 19 members of this prestigious society among its faculty, more than all others in Texas combined.

Dr. Parada directs the Kent Waldrep Center for Basic Research on Nerve Growth and Regeneration and holds the Southwestern Ball Distinguished Chair in Nerve Regeneration Research and the Diana K. and Richard C. Strauss Distinguished Chair in Developmental Biology.

His research integrates the fields of molecular genetics, embryonic development and signal transduction. His studies have provided critical insights into brain development, associated disorders and cancer biology, and have led to the identification of molecules that inhibit nerve regeneration after injury.

His laboratory focuses on the regulatory pathways that control the complex process of

nervous system development and the consequences of inappropriate development, which can include behavioral and mood disorders, as well as cancer.

SUMMER 2011

BEUTLER RETURNS; BECOMES UTSW'S 5TH NOBEL LAUREATE

Dr. Bruce Beutler, an internationally recognized leader in immunology and member of the National Academy of Sciences, was selected as the founding director of a new Center for the Genetics of Host Defense at UT Southwestern. His anticipated arrival was

quickly followed by news of his winning the Shaw Prize, sometimes referred to as the "Nobel Prize of the East." That recognition was followed by the ultimate honor for Dr. Beutler the 2011 Nobel Prize in Physiology or Medicine.

Dr. Beutler and Dr. Jules A. Hoffmann of Strasbourg University's Institut de Biologie Moléculaire et Cellulaire in France shared half the Nobel Prize for their discovery of receptor proteins that recognize disease-causing agents and activate innate immunity, the first step in the body's immune response. The other half went to the late Dr. Ralph M. Steinman of Rockefeller University in New York.

Dr. Beutler, who started his scientific career at UT Southwestern as an internal medicine intern and neurology resident, served as a faculty member from 1986 to 2000. Dr. Beutler made his seminal discoveries at UT Southwestern while searching for a receptor able to bind the bacterial product



lipopolysaccharide, which can cause life-threatening septic shock, a condition that involves overstimulation of the immune system.

Recruited from Scripps Research Institute in La Jolla, Calif., where he has developed one of the most robust gene discovery programs in the world, Dr. Beutler has focused on the genetics of innate immunity. The implications of his findings are broadly relevant to host responses to viral infection, cancer development and autoimmunity.

UT Southwestern faculty members now have won five Nobel Prizes since 1985. Dr. Michael Brown and Dr. Joseph Goldstein (1985), Dr. Johann Deisenhofer (1988), Dr. Alfred Gilman (1994) and Dr. Beutler (2011) have been honored by the Nobel Assembly at Karolinska Institutet in Sweden.

[See story Page 26]

PRESIDENT'S RESEARCH COUNCIL HONORS SCIENTISTS WITH DISTINGUISHED YOUNG RESEARCHER AWARDS

The President's Research Council presented its 2011 Distinguished Young Researcher Award to a pair of outstanding UT Southwestern investigators. The recipients – Dr. Kevin Choe, assistant professor of radiation



DR. KEVIN DR. SHUSHENG CHOE WANG

oncology, and Dr. Shusheng Wang, assistant professor of ophthalmology and pharmacology – each received a \$65,000 award.

Dr. Choe said PRC support will enable him to make meaningful contributions to the understanding of glioma biology as he seeks to identify potential therapeutic targets for malignant gliomas, the most common type of brain cancer in adults. Malignant gliomas are notoriously resistant to conventional therapy, Dr. Choe said.

Dr. Choe earned a doctorate in cell biology and a medical degree from the Albert Einstein College of Medicine in 2005 after receiving a degree in biology from the Massachusetts Institute of Technology in 1997. He completed an internship at Yale University and residency at the University of Chicago before joining the UT Southwestern faculty in 2010.

Dr. Wang is investigating the role of microRNAs in retinal vascular development and disease, focusing on how they regulate multiple pathways in age-related macular degeneration (AMD). His research has therapeutic implications for neovascular AMD, the leading cause of blindness in the elderly. AMD affects about 2 million people in the U.S.

Dr. Wang received his doctoral degree in developmental biology from Tulane University after earning a master's degree in cell biology from Peking University in Beijing. He went on to do postdoctoral work in molecular biology at UT Southwestern before joining the faculty in 2009.

The Distinguished Young Researcher Award is presented annually by the PRC, which is made up of community leaders who are interested in learning about and advancing medical research at UT Southwestern.

365 EARN DEGREES FROM THREE SCHOOLS

Diplomas were received by 207 UT Southwestern Medical School students and 42 UT Southwestern Graduate School of Biomedical Sciences students in June

commencement ceremonies. In mid-December 2010, 116 students graduated from the UT Southwestern School of Health Professions. The commencement ceremony, over which dean Dr. Raul Caetano presided, took place in the Tom and Lula Gooch Auditorium. Dr. Francisco G. Cigarroa, chancellor of the UT System and



DR. GEORGE "GEOF" LEBUS (RIGHT) RECEIVES THE HO DIN AWARD FROM W. PLACK CARR JR. EXECUTIVE VICE PRESIDENT OF SOUTHWESTERN MEDICAL FOUNDATIO

1983 graduate of UT Southwestern Medical School, addressed the medical school graduates and guests. The graduate school's address was delivered by Dr. Melanie Cobb, professor of pharmacology and former dean of the school.

Southwestern Medical Foundation's Ho Din Award, the top graduating medical student award, was presented to Dr. George "Geof" LeBus. Ying Liu received the Nominata Award, given to the outstanding graduate school student.

Dr. Daniel K. Podolsky, president of the medical center, conferred the degrees, diplomas and certificates to all of the medical, graduate and health professions students.

U.S. NEWS AGAIN CITES CARE AREAS IN 'BEST HOSPITALS'

For the second year in a row, UT Southwestern is the topranked hospital in the Dallas-Fort Worth region, according to U.S. News & World Report's annual ranking of the nation's best hospitals.

UT Southwestern earned its No. 1 ranking by being

Disorders.

nationally recognized in six specialties: urology, cardiology/heart surgery, diabetes/endocrinology, gynecology, nephrology and neurology/neurosurgery. The magazine also rated UT Southwestern as high-performing in six specialties: cancer, ear/nose/throat, gastroenterology, geriatrics, orthopaedics and pulmonology.

Dr. Daniel K. Podolsky, president of UT Southwestern, said the ratings acknowledge UT Southwestern's University Hospitals & Clinics' place among the nation's leading medical institutions in providing exceptional care to patients while remaining committed to groundbreaking research and academically preparing the next generation of caregivers and scientists.

Since 1990, U.S. News & World Report has identified the nation's elite medical centers with its annual "America's Best Hospitals" edition. The magazine produces rankings in 16 specialties. In 12 of the 16 specialties, the magazine factored in reputation, mortality index, patient safety index and other elements, such as nurse staffing ratios and trauma center designations. In the other four specialties the magazine went by reputation alone, determined by a nationwide survey of physicians.

APPOINTMENTS FOR 2010-2011

The following individuals were appointed to endowed positions or to major leadership positions at UT Southwestern during the past fiscal year.

Peggy Bailey, assistant vice president/accreditation and clinical support services for University Hospitals.

Dr. Bruce Beutler, director of the Center for the Genetics of Host Defense and to the Raymond and Ellen Willie Distinguished Chair in Cancer Research, in Honor of Laverne and Raymond Willie Sr.

Dr. Ilya Bezprozvanny, to the Carl J. and Hortense M. Thomsen Chair in Alzheimer's Disease Research.

John A. Brandecker, chief operating officer for University Hospitals.

Dr. Elizabeth "Beth" Brickner, to the Charles B. Mullins, M.D., Professorship in Clinical Practice and Teaching in Cardiology.

Dr. Brian Casey, to the Gillette Professorship in Obstetrics and Gynecology.

Dr. Zhijian "James" Chen, to the George L. MacGregor Distinguished Chair in Biomedical Science.

Dr. Susan M. Cox, regional dean - Austin programs.

Dr. Ponciano Cruz, to the Paul R. Bergstresser, M.D., Chair in Dermatology.

Dr. Byron Cryer, associate dean for faculty diversity and development.

Dr. Jef De Brabander, to the Julie and Louis Beecherl Jr. Chair in Medical Science.

Dr. Joel Elmquist, to the Carl H. Westcott Distinguished Chair in Medical Research.

Lynn Fischer, associate vice president/cardiovascular services, and surgical services for University Hospitals.

Dr. Abhimanyu Garg, to the Distinguished Chair in Human Nutrition Research.

Dr. Elizabeth Goldsmith. to the Patti Bell Brown Professorship in Biochemistry.

Dr. Yu-Guang He, to the Josephine Long Biddle Chair in Age-Related Macular Degeneration Research.

Dr. Lora Hooper, to the J. Wayne Streilein, M.D., Professorship in Immunology.

Dr. Mustafa Husain, to the Lydia Bryant Test Distinguished Professorship in Psychiatric Research.

Dr. Michael Jessen, chairman of cardiovascular and thoracic surgery and to the Frank M. Ryburn Jr. Distinguished Chair in Cardiothoracic Surgery and Transplantation.

Rashard Johnson, assistant vice president/non-clinical support services for University Hospitals.

Dr. Ege Kavalali, to the Rosewood Corporation Chair in Biomedical Science.

Dr. Kemp Kernstine, to the Robert Tucker Hayes Foundation Distinguished Chair in Cardiothoracic Surgery.

Dr. George Lister, associate dean for education.

Dr. James Malter, to the Senator Betty and Dr. Andy Andujar Distinguished Chairmanship of Pathology.

Dr. David Mangelsdorf, to the Raymond and Ellen Willie Distinguished Chair in Molecular Neuropharmacology, in Honor of Harold B. Crasilneck. Ph.D.

Dr. Bradley F. Marple, assistant dean, graduate medical education.

Becky McCulley, associate vice president for clinical program development.

Mike Medina, associate vice president for University Hospitals clinical support services.

Dr. Ronald Mitchell, to the William Beckner, M.D., Distinguished Chair in Otolaryngology.

Dr. Sean Morrison, director of the Children's Research Institute at UT Southwestern and to the Mary McDermott Cook Chair in Pediatric Genetics.

Dr. Shawna Nesbitt, associate dean of minority student affairs.

Dr. Jerry Niederkorn, to the Royal C. Miller Chair in Age-Related Macular Degeneration Research.

Dr. Orhan Oz, to the Wechun Pak Professorship of Bone Biophysics.

Dr. Amit Pandya, to the Dr. J.B. Shelmire Professorship in Dermatology.

Donna Richardson, associate vice president and chief nursing officer for University Hospitals.

Dr. Claus Roehrborn, to the S.T. Harris Family Chair in Medical Science, in Honor of John D. McConnell, M.D.

Dr. Peter Roland. to the Beth and Marvin C. (Cub) Culbertson Professorship in Pediatric Otolaryngology.

Dr. Michael Roth, interim dean of UT Southwestern Graduate School of Biomedical Sciences

Dr. David Russell, vice provost and dean of basic research.

Dr. Arthur Sagalowsky, master of Cary College. ■ Michael Serber, vice

president for financial affairs. Dr. Philip Shaul, to the

Associates First Capital Corporation Distinguished Chair in Pediatrics.

Dr. Stephen Skapek, to the Children's Cancer Fund Distinguished Professorship in Pediatric Oncology Research. Dr. John Sweeney, to the Townsend Distinguished Chair

Dr. Robert Toto, director of Dr. Kosaku Uyeda, to the Dr. James "Jim" Valentine, Dr. John Warner, assistant Dr. George Wendel, to the Dr. Michael White. to the Dr. Charles Whitten, to the

development. the Houston J. and Florence A. Doswell Center for the Development of New Approaches for the Treatment of Hypertension and associate dean, translational science. Bonnie Bell Harding Professorship in Biochemistry. chairman of the Division of Vascular Surgery in the Department of Surgery. vice president for University Hospitals planning. Norman F. Gant Jr., M.D., Chair in Obstetrics and Gynecology. Grant A. Dove Chair for Research in Oncology. Margaret Milam McDermott Distinguished Chair in

Anesthesiology and Pain Management.

Dr. Charles Preston Wiles Jr., to the Drs. Anne and George Race Professorship of Student Psychiatry.

Dr. DuWayne Willett, chief medical informatics officer, health system.

Angela Wishon, vice president for research administration.

Dr. Richard Wu. to the L. David Hillis, M.D., Professorship in Clinical Research in Cardiology.

MAJOR GIFTS IN 2010-2011

Philanthropists continued to demonstrate their commitment to UT Southwestern in 2010-2011, providing support for a variety of research, clinical and educational programs.

in Research on Autism Spectrum

Dr. Dwain Thiele, senior associate dean for strategic

Major new pledges and gifts received in the fiscal year 2010-2011 included:

\$13,413,530 from an anonymous donor to support research and patient care programs at UT Southwestern.

■ \$10.261.000 from Mrs. Eugene McDermott, including \$10,161,000 to Southwestern Medical Foundation to support the construction of UT Southwestern's new University Hospital and \$100.000 to UT Southwestern to further research on Fragile X Syndrome under the direction of Dr. Kimberly Huber.

\$5,000,000 from an anonymous donor to Southwestern Medical Foundation to support the construction of UT Southwestern's new University Hospital.

■ \$5,000,000 from Robert and Terry Rowling to Southwestern Medical Foundation to support the construction of UT Southwestern's new University Hospital.

■ \$3,000,000 from the Harlan R. Crow family. Trammell S. Crow family and Stuart M. Crow family to support the construction of UT Southwestern's new University Hospital.

■ \$2,000,000 from an anonymous donor to support research into the causes, prevention and treatment of heart failure.

■ \$2,000,000 from the Hoblitzelle Foundation to Southwestern Medical Foundation to support the construction of UT Southwestern's new University Hospital.

■ \$1,617,984 from proceeds of the 2010 Sweetheart Ball to Southwestern Medical Foundation in support of heart research at UT Southwestern.

■ \$1,233,000 from the David M. Crowley Foundation, including \$1,000,000 to Southwestern Medical

Foundation to support the construction of UT Southwestern's new University Hospital and \$233,000 to UT Southwestern to support research in the areas of breast cancer, spinal cord injury, Parkinson's disease, and peripheral nerve and pain management.

■ \$1,125,000 from Sam Y. Dorfman, Jr., M.D., and Louis Dorfman, Sr., including \$1,000,000 to Southwestern Medical Foundation to support the construction of UT Southwestern's new University Hospital and \$125,000 to UT Southwestern to support clinical research programs.

■ \$1,025,000 from the A.L. Chilton Foundation to Southwestern Medical Foundation to support the construction of UT Southwestern's new University Hospital, establish the Patti Bell Brown Professorship in Biochemistry, establish the Bonnie Bell Harding Professorship in Biochemistry, provide five post-doctoral research fellowships in biochemistry and continue support for the Chilton Visiting Lectureship.

\$1,000,000 from an anonymous donor to Southwestern Medical Foundation to support the construction of UT Southwestern's new University Hospital.

■ \$1,000,000 from the Kenneth C. English Family Foundation to Southwestern Medical Foundation to support the construction of UT Southwestern's new University Hospital.

■ \$1,000,000 from Ute Schwarz and Rolf R. Haberecht to Southwestern Medical Foundation to support the construction of UT Southwestern's new University Hospital.

\$1,000,000 from Sandi and Ron W. Haddock to Southwestern Medical Foundation to support the construction of UT Southwestern's new University Hospital.

\$1,000,000 from Nancy B. Hamon, through a bequest to Southwestern Medical Foundation, to support the construction of UT Southwestern's new University Hospital.

■ \$1,000,000 from Linda W. and Mitch Hart to Southwestern Medical Foundation to support the construction of UT Southwestern's new University Hospital

■ \$1,000,000 from the Hawn Foundation, Inc., to Southwestern Medical Foundation to support the construction of UT Southwestern's new University Hospital.

■ \$1,000,000 from the Hirsch Family Foundation to Southwestern Medical Foundation to support the construction of UT Southwestern's new University Hospital.

■ \$1,000,000 from the **Eugene McDermott Foundation** to Southwestern Medical Foundation to support the construction of UT Southwestern's new University Hospital.

■ \$1,000,000 from Once Upon a Time... to support the Low Birth Weight Clinic and programs in pediatric neurodevelopment.

■ \$1,000,000 from the Ralph B. Rogers Foundation to Southwestern Medical Foundation to support the construction of UT Southwestern's new University Hospital.

■ \$1,000,000 from Mr. and Mrs. Edward W. Rose III to Southwestern Medical

Foundation to support the construction of UT Southwestern's new University Hospital.

■ \$1,000,000 from William T. and Gay F. Solomon to Southwestern Medical Foundation to support the construction of UT Southwestern's new University Hospital.

■ \$1,000,000 from Jean and Tom Walter to Southwestern Medical Foundation to support the construction of UT Southwestern's new University Hospital.

■ \$900,000 from The Lupe Murchison Foundation to support Alzheimer's disease research.

\$600,000 from the Mary Kay Family Foundation and Mary Kay, Inc., including \$500,000 to Southwestern Medical Foundation to support the construction of UT Southwestern's new University Hospital and \$100,000 to UT Southwestern to support breast cancer research.

■ \$515,392 from the Rose S. Van Wert Trust to Southwestern Medical Foundation to provide unrestricted support for UT Southwestern.

■ \$510,535 from the Mary R. Saner Charitable Remainder Annuity Trust to support patient assistance programs at UT Southwestern University Hospital – St. Paul.

\$500,000 from an anonymous donor to Southwestern Medical Foundation to provide unrestricted support for UT Southwestern.

\$500,000 from St. Paul Medical Foundation to support the construction of UT Southwestern's new University Hospital.

■ \$425,000 from the Hartwell Foundation to provide individual and collaborative

biomedical research fellowships for promising early-career investigators at UT Southwestern

\$417,925 from Mary Frances King, through a bequest to Southwestern Medical Foundation, to advance cancer research at UT Southwestern.

\$400,000 from the Doris Duke Charitable Foundation to Southwestern Medical Foundation to support the Doris Duke Clinical Research Fellowship Program for Medical Students at UT Southwestern.

\$350,000 from an anonymous donor to support multiple sclerosis research under the direction of Dr. Elliot Frohman.

\$344,000 from the NIWA Institute for Pharmacology to support research of rheumatic diseases under the direction of Dr. Joel D. Taurog.

■ \$300,000 from the National Multiple Sclerosis Society to support the Multiple Sclerosis Program and Clinical Center at UT Southwestern.

■ \$274,132 from Lovse J. Quinlan, through a bequest to St. Paul Medical Foundation, in support of clinical programs at UT Southwestern University Hospital – St. Paul.

■ \$250,000 from the William Davidson Foundation to support the Jonathan W. Uhr, M.D., Distinguished Chair in Immunology.

■ \$250,000 from Mrs. S. T. Harris to support a fund to honor Kern Wildenthal, M.D., Ph.D.

■ \$250,000 from Rollin W. King to Southwestern Medical Foundation to support the construction of UT Southwestern's new University Hospital.

■ \$250,000 from Dr. Gerard Noteboom, through a bequest to Southwestern Medical Foundation, to establish the Elizabeth Haaland, M.D., and

Gerard Noteboom, M.D., **Endowed Medical Scientist** Training Program Scholarship Fund; the Elizabeth Haaland, M.D., Endowed Fund for Clinical Care in Dermatology; the Gerard Noteboom, M.D., Endowed Fund for Clinical Care in Pathology; and the Gerard Noteboom, M.D., Endowed Fund for Stem Cell Research.

Generous contributions and pledges of \$100,000 to \$249,999 were received from a number of additional donors, including the following new commitments from:

■ Mr. and Mrs. Edward M. Ackerman to Southwestern Medical Foundation to support a variety of programs at UT Southwestern.

An anonymous donor to support UT Southwestern's Patient Navigator Program, as well as lung cancer research and patient care programs in honor of Drs. Hak Choy, J. Michael DiMaio, Jonathan E. Dowell and David A. Pistenmaa. The Kent & JoAnn Foster

Family Foundation to support research aimed at defining better treatment of Type 1 diabetes.

Gayden Family Foundation to Southwestern Medical Foundation to provide unrestricted support for UT Southwestern.

■ Mr. and Mrs. Mark D. Gibson to Southwestern Medical Foundation to provide unrestricted support for UT Southwestern.

Felix B. and Josephine I. Goldman, through a testamentary gift to Southwestern Medical Foundation, to support scholarships for medical students attending UT Southwestern Medical School. Harry and Rosemary Holcomb Living Trust to support

Alzheimer's disease research.

David M. Marshall, through a bequest, to support programs in medical research, education and clinical care.

Catherine & James McCormick Foundation to establish the Catherine & James McCormick Charitable Foundation Fund in Aging.

Wm A & Elizabeth B Moncrief Foundation to support activities in UT Southwestern's Department of Plastic Surgery.

The Muscular Dystrophy Association to support ALS research.

The Ted Nash Long Life Foundation to advance Alzheimer's disease research.

The Charles Y.C. Pak Foundation to support research conducted by the Neill Walsdorf, Sr. Biotechnology Center in Mineral Metabolism and the Charles and Jane Pak Center for Mineral Metabolism and Clinical Research.

Rudman Securities to provide support for the Josephine Rudman Laboratory for Alzheimer's Disease Research.

Dr. Donald C. Schenk to Southwestern Medical Foundation to support education, research and clinical care programs at UT Southwestern.

The Tom Thumb Foundation to support clinical trials for the treatment of breast cancer.

The West Endowment to support bone marrow transplantation and follicular lymphoma research.

Womack Machine Supply Company to support the activities of UT Southwestern's Patient and Guest Services.

